Osteoporosis in Childhood

22 ottobre 2015

- Prevention of Adult Osteoporosis
- Prevention of Childhood Osteoporosis
- Management of Childhood Osteoporosis

The Genetics of Bone Loss: Challenges and Prospects

Braxton D. Mitchell and Laura M. Yerges-Armstrong

Division of Endocrinology, Diabetes, and Nutrition, Department of Medicine, University of Maryland
School of Medicine, Baltimore, Maryland 21201

J Clin Endocrinol Metab, May 2011, 96(5):1258–1268

TABLE 2. Genes robustly associated with BMD on GWAS meta-analyses

Gene	Location	Full name
TGFBR3	1p22	TGF, β-receptor III
ZBTB40	1p36	Zinc finger and BTB domain containing 40
GPR177	1p31.3	G protein-coupled receptor 177 (aka WNTLESS homolog)
SPTBN1	2p21	Spectrin, β, nonerythrocytic 1
CTNNB1	3p22	catenin (cadherin-associated protein) β1
MEPE	4q21.1	matrix, extracellular phosphoglycoprotein; aka osteoblast/osteocyte factor 45
MEF2C	5q14	MADS box transcription enhancer factor 2, polypeptide C
ESR1	6q25	Estrogen receptor 1
C6orf97	6q25	Chromosome 6 open reading frame 97
STARD3NL	7p14	STARD3 N-terminal like, encodes a cholesterol endosomal transporter
SFRP4	7p14	Secreted frizzled-related protein 4
FLJ42280	7q21.3	Unknown function
FAM3C	7q31	Family with sequence similarity 3, member C
VPS13B	8q22	Vacuolar protein sorting-associated protein 13B
TNFRSF11B	8q24	TNF receptor superfamily, member 11b (encodes Opg)
ARHGAP1	11p11.2	ρ-GTPase activating protein 1
LRP5	11q13.4	low density lipoprotein receptor-related protein 5
DCDC5	11p14.1	doublecortin domain containing 1
SOX6	11p15	SRY (sex determining region Y)-box 6 (encodes a SOX family transcription factor defined by a conserved high-mobility group DNA-binding domain)
SP7	12q13	Osterix; Sp7 transcription factor
AKAP11	13q14	A kinase (PRKA) anchor protein 11
TNFSF11	13q14	TNF (ligand) superfamily, member 11 (RANKL)
ADAMTS18	16q23	ADAM metallopeptidase with thrombospondin type 1 motif, 18
FOXL1, FOXC2	16q24.3	Forkhead gene family, expressed in the gastrointestinal mucosa (FOXL1) or involved in adipocyte metabolism and early-stage chondrogenic differentiation (FOXC2)
SOST	17q11.2	Sclerostin
CRHR1	17q12-q22	CRF receptor
HDAC5	17q21	Histone deacetylase 5
TNFRSF11A	18q21	TNF receptor superfamily, member 11a, NFKB activator (encodes RANK)
JAG1	20p12	Protein jagged-1 precursor

Compiled from Refs. 37–41, 43–46.

Osteoporosis: now and the future

Tilman D Rachner, Sundeep Khosla, Lorenz C Hofbauer

***Lancet* 2011; 377: 1276–87**

A

B

Normal

Osteoporosis

C

Osteoclast

Osteoblast

1 10 µm

2 50 µm

3 100 µm

4 500 µm

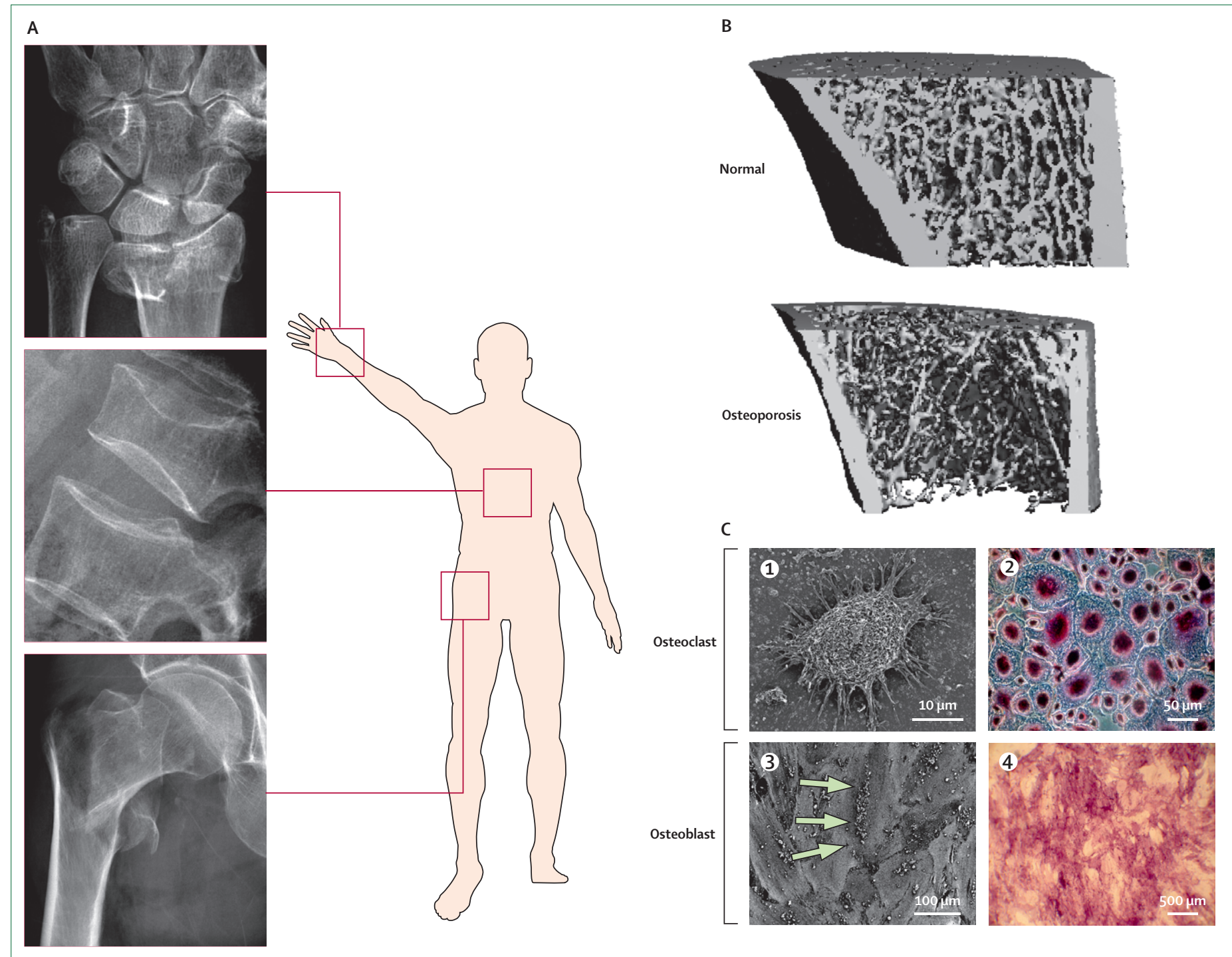
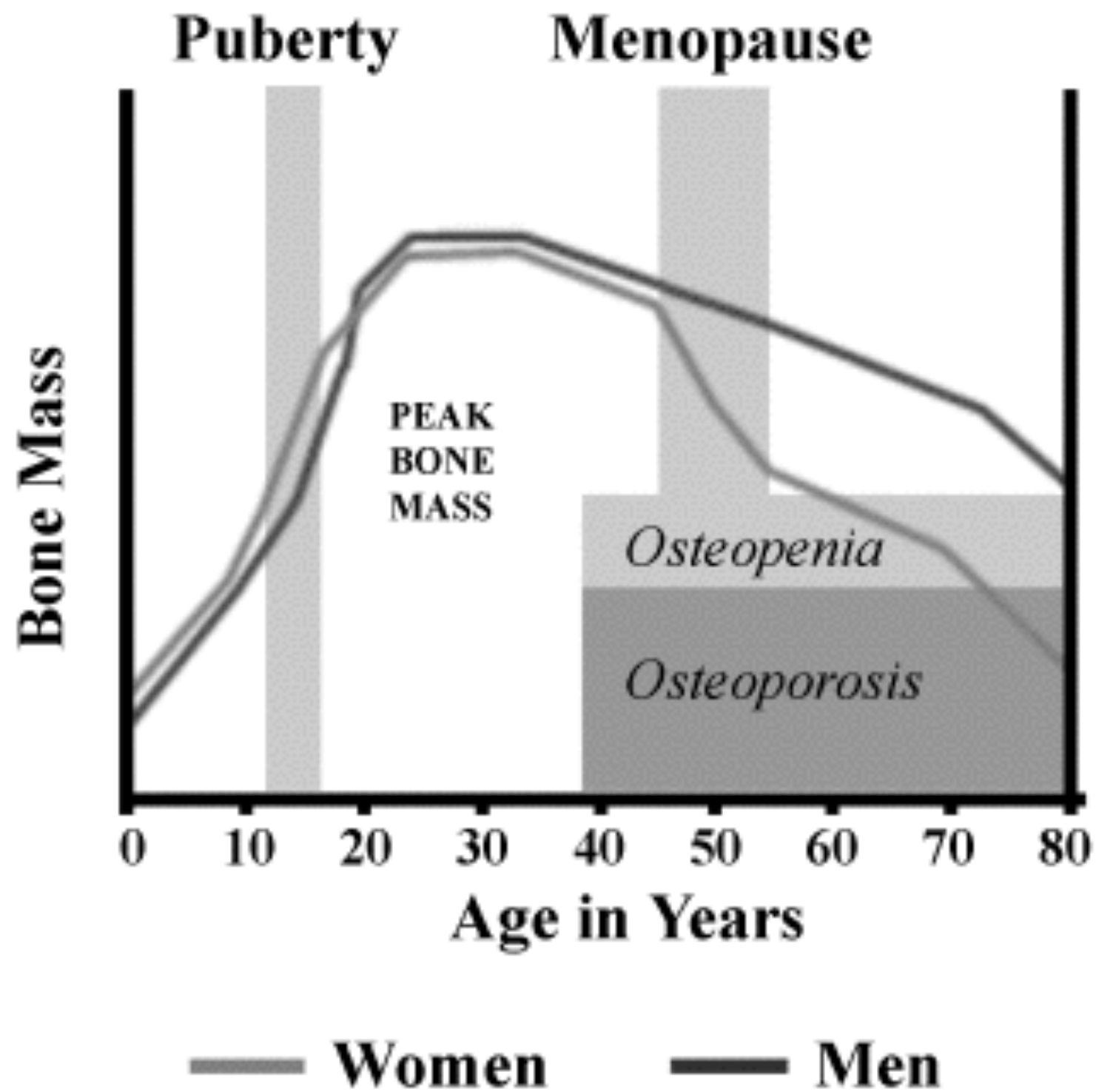



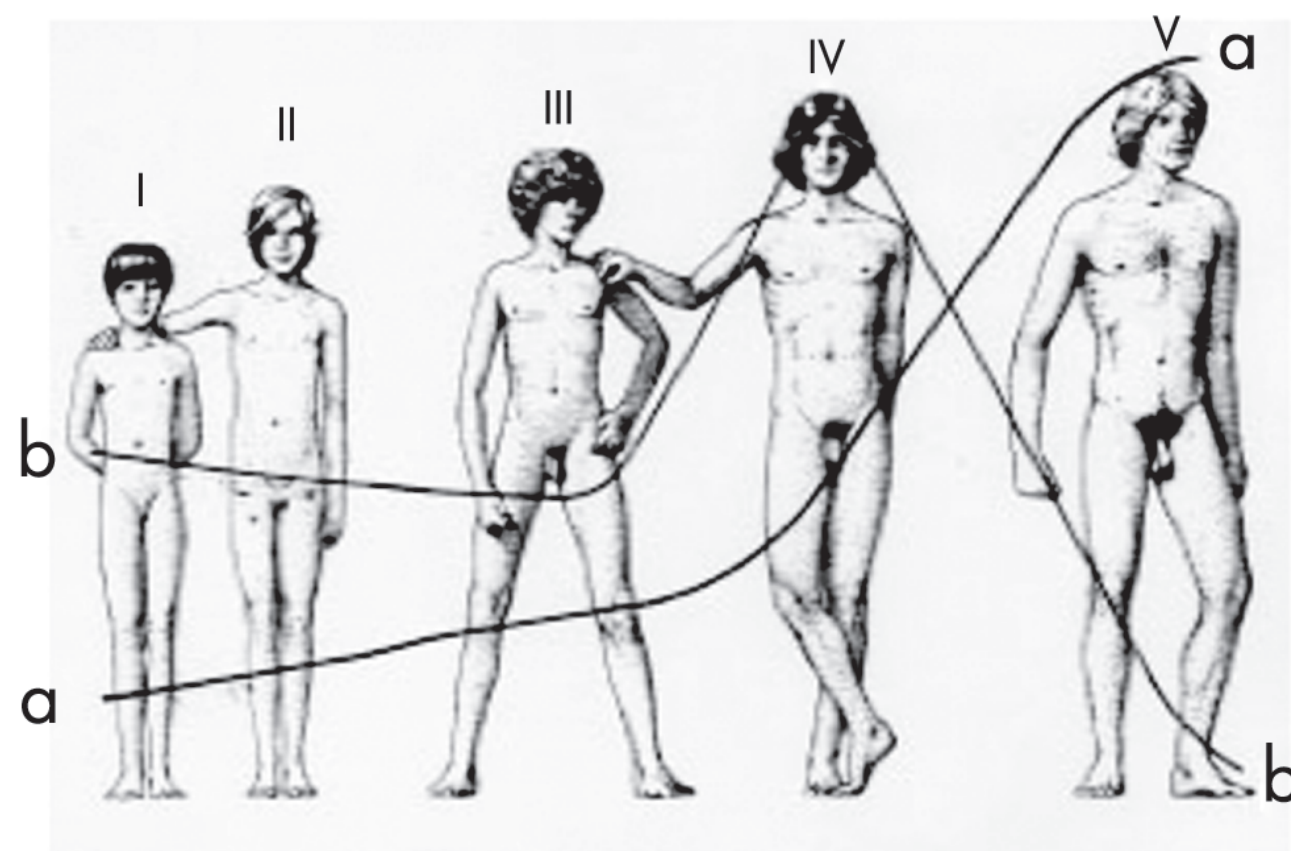
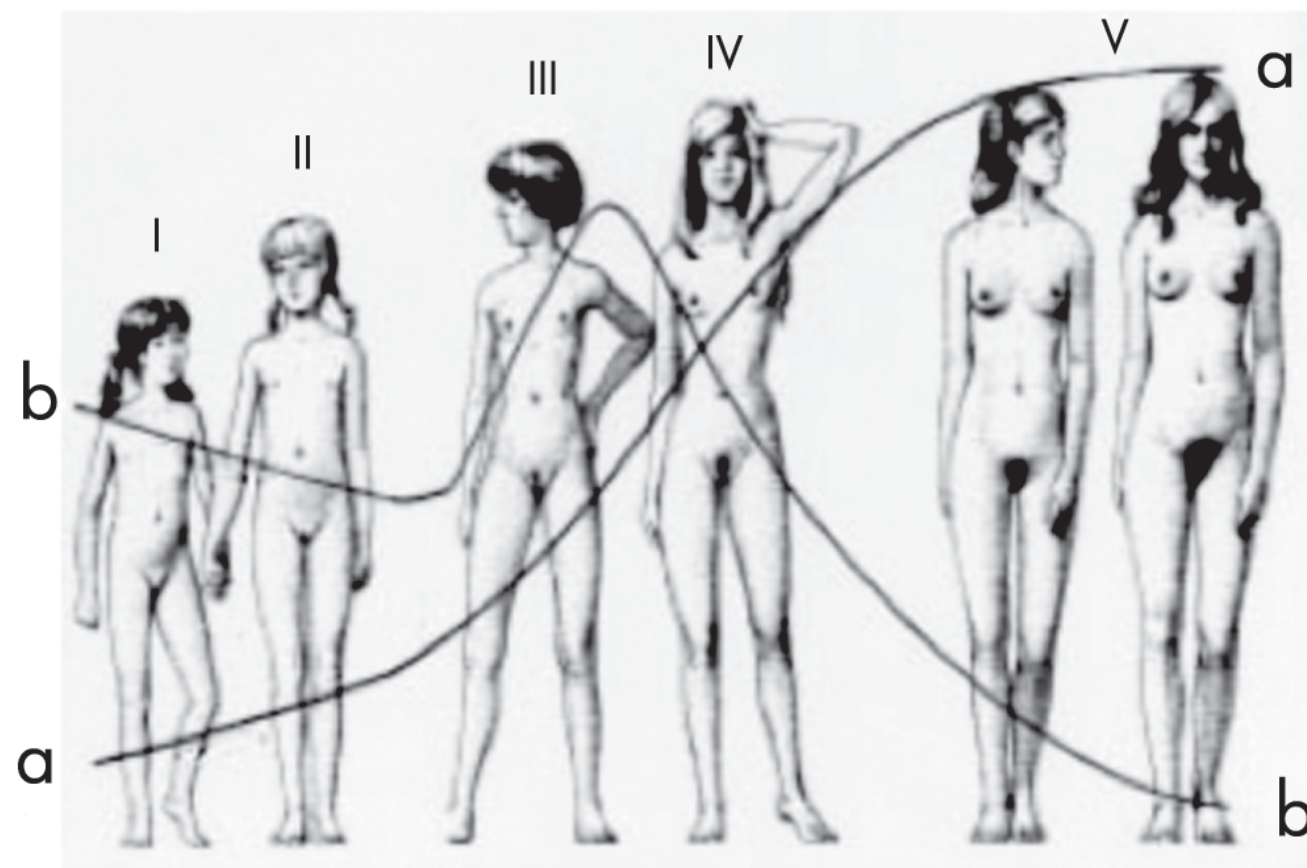
***Figure 1:* Osteoporosis at a glance**
Osteoporosis is a systemic skeletal disease in which bone resorption exceeds bone formation and results in microarchitectural changes. (A) Fragility fractures typically involve wrist, vertebrae, and hip. (B) Microcomputed tomography shows marked trabecular thinning of osteoporotic bone compared with normal bone. (C) Microscopic views of bone-resorbing osteoclasts and bone-forming osteoblasts: (1) osteoclast with its distinctive morphology; (2) tartrate-resistant acidic phosphatase staining of multinucleated osteoclasts; (3) multiple osteoblasts (white arrowheads) on mineralised matrix; (4) alkaline phosphatase staining of osteoblasts.

Bone Mass Lifecycle
Puberty
Menopause
Bone Mass
PEAK
BONE
MASS
Osteopenia
Osteoporosis
0
10
20
30
40
50
60
70
80
Age in Years
Women
Men

Pubertal Timing, Bone Acquisition, and Fracture Throughout Life

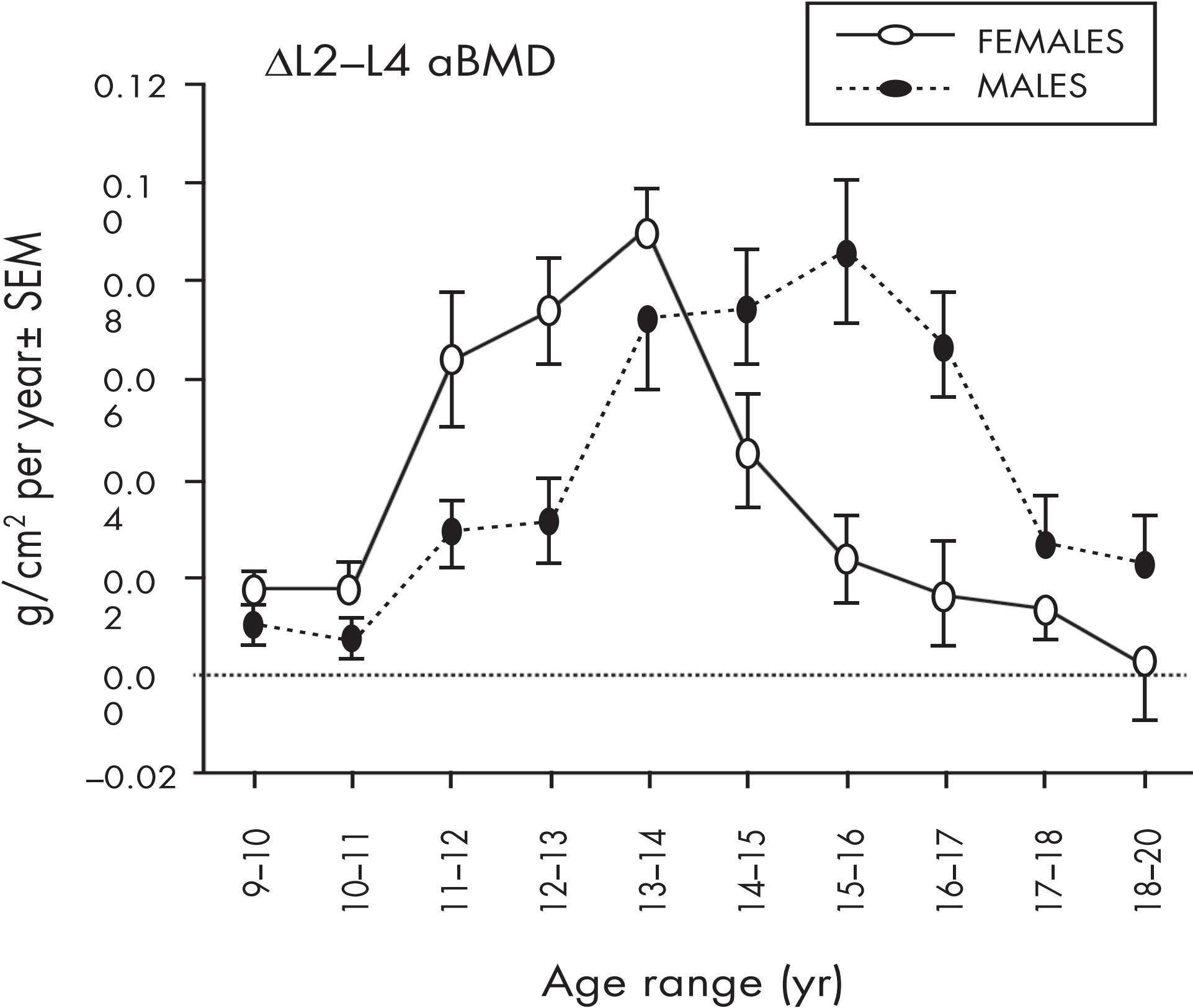
Jean-Philippe Bonjour and Thierry Chevalley

Division of Bone Diseases, University Hospitals and Faculty of Medicine, CH-1211 Gen

(*Endocrine Reviews* 35: 820–847, 2014)

2014 Bonjour Puberty Bone

Pubertal Timing, Bone Acquisition, and Risk of Fracture Throughout Lif-

Jean-Philippe Bonjour and Thierry Che
Division of Bone Diseases, University Hospitals and

(*Endocrine Review*

2014 Bonjour I

Diagnosi e terapia dell'**osteoporosi** in **età evolutiva**

Tabella 1. Massa ossea: fattori implicati

Genetici	• Genere
	• Razza
	• Famigliarità
	• Polimorfismi genetici dei seguenti geni candidati: VDR, COLIA1, ESR, IGF-I, IL-6, TGFβ, LRP5, Leptina, BMP2
Endocrini	• GH/IGF-I
	• Androgeni surrenalici
	• Estrogeni
	• Testosterone
Meccanici	• Massa muscolare
	• Attività fisica
Nutrizionali	• Diete inadeguate e selettive
	• Calcio
	• Vitamina D
Altro	• Terapie farmacologiche
	• Malattie croniche
	• Alcol
	• Fumo

BMP2= bone morphogenetic protein-2; COLIA1= collagene di tipo 1; ESR= recettore degli estrogeni; IGF-I= insulin-like growth factor 1; IL-6= interleuchina 6; LRP5= lipoprotein receptor related protein-5; TGF-β= transforming growth factor beta; VDR= recettore della vitamina D.

Antoniazzi F.
Informer in Endocrinologia, 2010; 13: 6-13

Osteoporosis in Childhood

1. Definition
2. When to suspect Osteoporosis
   2.1. Fractures
   2.2. Primary osteoporosis
   2.3. Secondary Osteoporosis
3. Prevention
4. Management
5. Pharmacological treatment
6. Conclusions

Fracture Prediction and the Definition of Osteoporosis in Children and Adolescents

- Evaluation of bone health should identify children and adolescents who may benefit from interventions to decrease their elevated risk of a clinical significant fracture.
- The finding of 1 or more vertebral compression (crush) fractures is indicative of osteoporosis, in the absence of local disease or high energy trauma. In such children and adolescents, measuring bone mineral density (BMD) adds to the overall assessment of bone health.
- The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone.
- In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score of 2.0 or lower.

A clinically significant fracture history is one or more of the following:

(1) 2 or more long-bone fractures by the age of 10 yr;

(2) 3 or more long-bone fractures at any age up to age 19 yr.

A bone mineral content (BMC)/BMD Z- score higher than 2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.

2 - When to suspect osteoporosis

- Fractures
- Primary osteoporosis
- Secondary Osteoporosis

Osteoporosi Pediatrica

Popolazioni a rischio

- malattie croniche genetiche o acquisite
- immobilità
- inadeguata nutrizione

2.1 - Fractures

Fractures in children and adolescents

- Overall risk of sustaining a fracture during childhood is almost 50% for boys and 30% for girls.
- Boys and girls have a similar fracture incidence up to the age of 10 years; thereafter, boys sustain substantially more fractures than girls, and twothirds of all childhood fractures occur in boys.
- The fracture incidence is highest during pubertal years and declines rapidly thereafter.
- Furthermore, the prevalence of upper limb fractures in children has increased

ORIGINAL ARTICLE JBMR

Decreasing Incidence and Changing Pattern of Childhood Fractures: A Population-Based Study

Mervi K Mäyränpää,[1] Outi Mäkitie,[2] and Pentti E Kallio[1]

[1]Department of Pediatric Surgery, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland
[2]Department of Pediatrics, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

Journal of Bone and Mineral Research, Vol. 25, No. 12, December 2010, pp 2752–2759

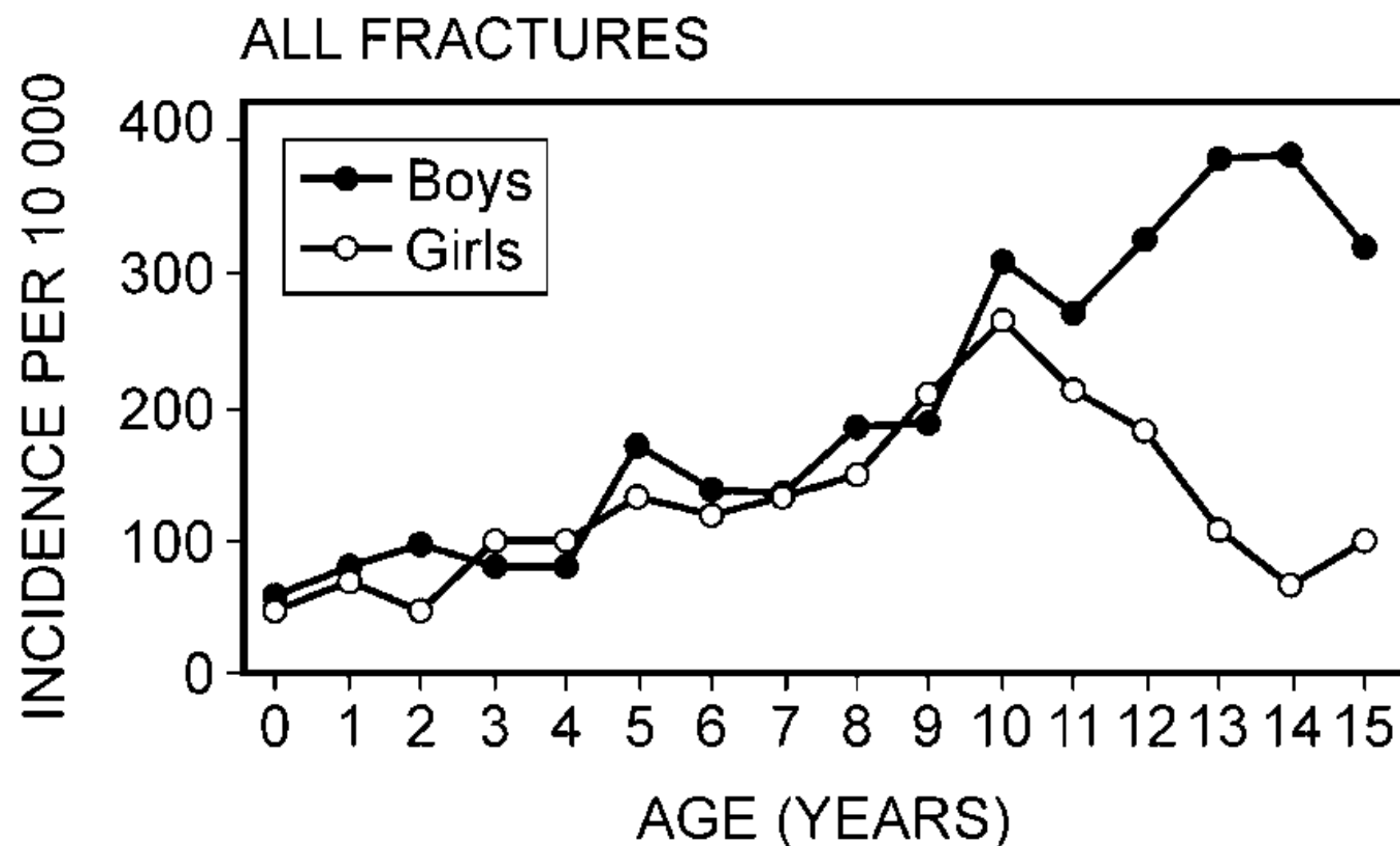



Fig. 1. Annual incidence of all fractures in children by age and sex. Children aged 0 to 15 years, 2005, in Helsinki, Finland. Total number of fractures = 1396. Age in years. Incidence per 10,000.

ORIGINAL ARTICLE JBMR

Decreasing Incidence and Changing Pattern of Childhood Fractures: A Population-Based Study

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[1]Department of Pediatric Surgery, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland
[2]Department of Pediatrics, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

Journal of Bone and Mineral Research, Vol. 25, No. 12, December 2010, pp 2752–2759
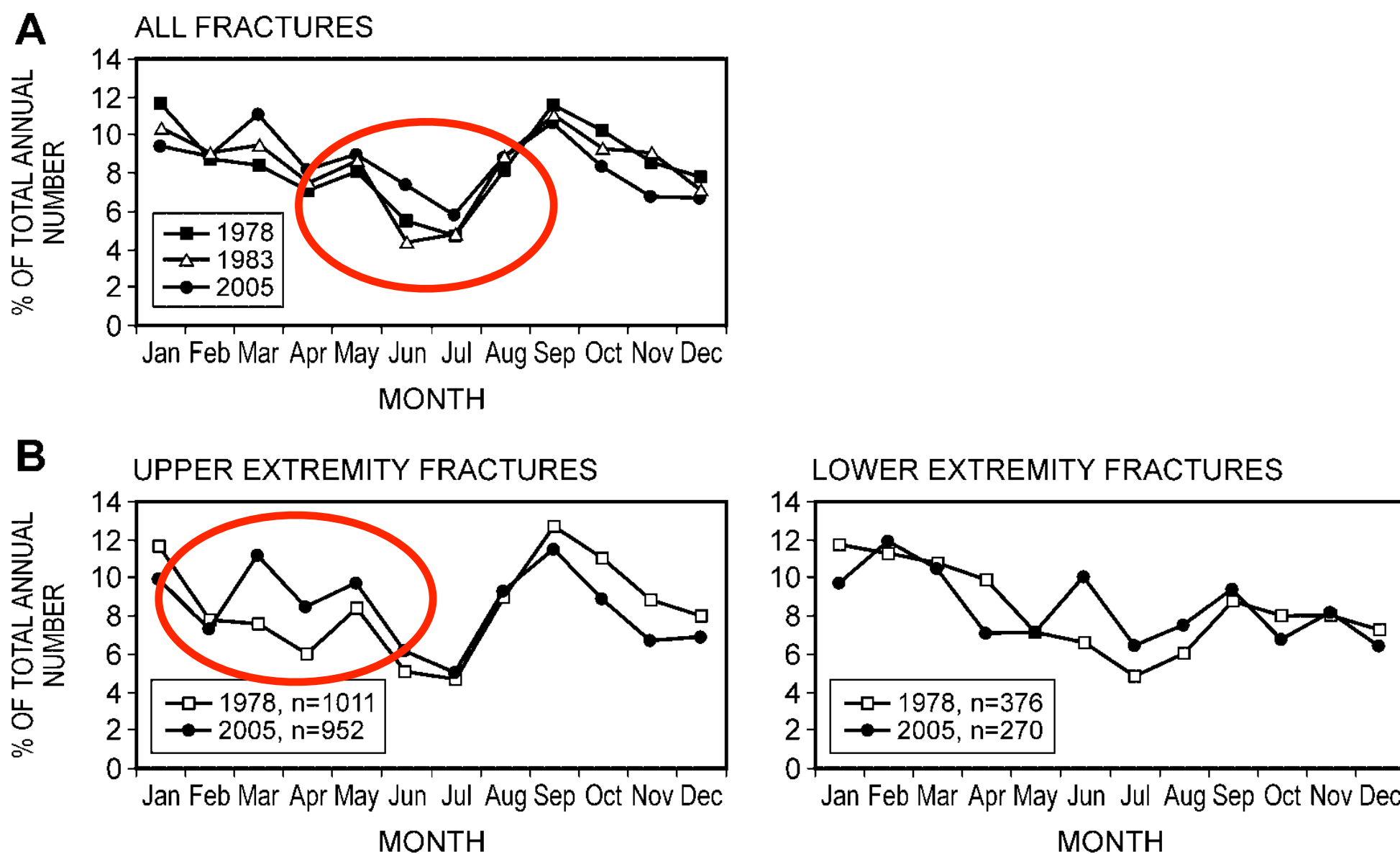
Fig. 2. Seasonal variation of traumas. Children aged 0 to 14 years, in Helsinki, Finland. (*A*) Distribution of extremity fractures in 1978, all pediatric injuries in 1983, and all pediatric fractures in 2005. (*B*) Distribution of upper extremity and lower extremity fractures in 1978 and 2005 by month.

ORIGINAL ARTICLE JBMR

Decreasing Incidence and Changing Pattern of Childhood Fractures: A Population-Based Study

Mervi K Mäyränpää,[1] Outi Mäkitie,[2] and Pentti E Kallio[1]
[1]Department of Pediatric Surgery, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland
[2]Department of Pediatrics, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

Journal of Bone and Mineral Research, Vol. 25, No. 12, December 2010, pp 2752–2759

Table 2. All Fractures in Children of 0 to 15 Years, in Helsinki, Finland, 2005

		All children					Boys	Girls
Fracture site	Diagnosis (ICD-10)	*n*	%	Incidence[a]	Age, median (years)	Males (%)	Incidence[a]	Incidence[a]
Skull	S02.0–S02.1	17	1.2	2.0	0.9	65	2.5	1.4
Face	S02.2–S02.7	33	2.4	3.9	12.3	64	4.8	2.9
Vertebra, cervical	S12.1–S12.2	1	0.1	0.1	12.2	0	0	0.2
Thoracic	S22.0–S22.1	13	0.9	1.5	11.6	69	2.1	1.0
Lumbar	S32.0, S32.7	2	0.1	0.2	12.3	0	0	0.5
Sternum	S22.2	1	0.1	0.1	13.7	0	0	0.2
Rib(s)	S22.3–S22.4	1	0.1	0.1	7.6	0	0	0.2
Pelvis	S32.3–S32.7	4	0.3	0.5	13.0	75	0.7	0.2
Clavicle	S42.0	89	6.4	10.4	6.2	66	13.5	7.1
Scapula	S42.1	1	0.1	0.1	15.1	100	0.2	0
Humerus, proximal	S42.2	34	2.4	4.0	12.0	53	4.1	3.8
Diaphyseal	S42.3	5	0.4	0.6	1.9	100	1.1	0
Distal	S42.4	84	6.0	9.8	6.4	52	10.1	9.5
Radius/ulna, proximal	S52.0–S52.1	34	2.4	4.0	10.7	56	4.4	3.6
Diaphyseal	S52.2–S52.4	58	4.2	6.8	8.5	62	8.3	5.2
Distal	S52.5–S52.8	425	30.4	49.6	10.9	64	62.7	36.1
Wrist bones	S62.0–S62.1	4	0.3	0.5	13.6	75	0.7	0.2
Metacarpals	S62.2–S62.4	63	4.5	7.4	12.9	87	12.6	1.9
Fingers	S62.5–S62.7	227	16.3	26.5	11.4	66	34.2	18.5
Femur	S72.0–S72.4	24	1.7	2.8	7.3	58	3.2	2.4
Patella	S82.0	7	0.5	0.8	14.0	57	0.9	0.7
Tibia/fibula, proximal	S82.1	14	1.0	1.9	6.1	64	2.1	1.2
Diaphyseal	S82.2, S82.4	24	1.7	2.8	9.1	50	2.8	2.9
Distal	S82.3	29	2.1	3.4	12.3	62	4.1	2.6
Malleoli	S82.5–S82.8	60	4.3	7.0	11.2	55	7.6	6.4
Tarsal bones	S92.0–S92.2	9	0.6	1.1	9.1	67	1.4	0.7
Metatarsals	S92.3	71	5.1	8.3	10.8	58	9.4	7.1
Toes	S92.4–S92.5	62	4.4	7.2	12.4	53	7.6	6.9
All		1396	100	163.0	10.8	63	201.2	123.6

[a]Incidence per 10,000 population.

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available online at http://www.sciencedirect.com

1

Epidemiology of osteoporosis

Christopher Holroyd BM, MRCP
SpR in Rheumatology

Cyrus Cooper MA, DM, FRCP, FFPH, FMedSci
Professor of Rheumatology
Director, MRC Resource Centre, Southampton

Elaine Dennison* MB, BChir, MA, MRCP, MSc Phd
Reader and Honorary Consultant in Rheumatology
MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital,
Southampton SO16 6YD, UK
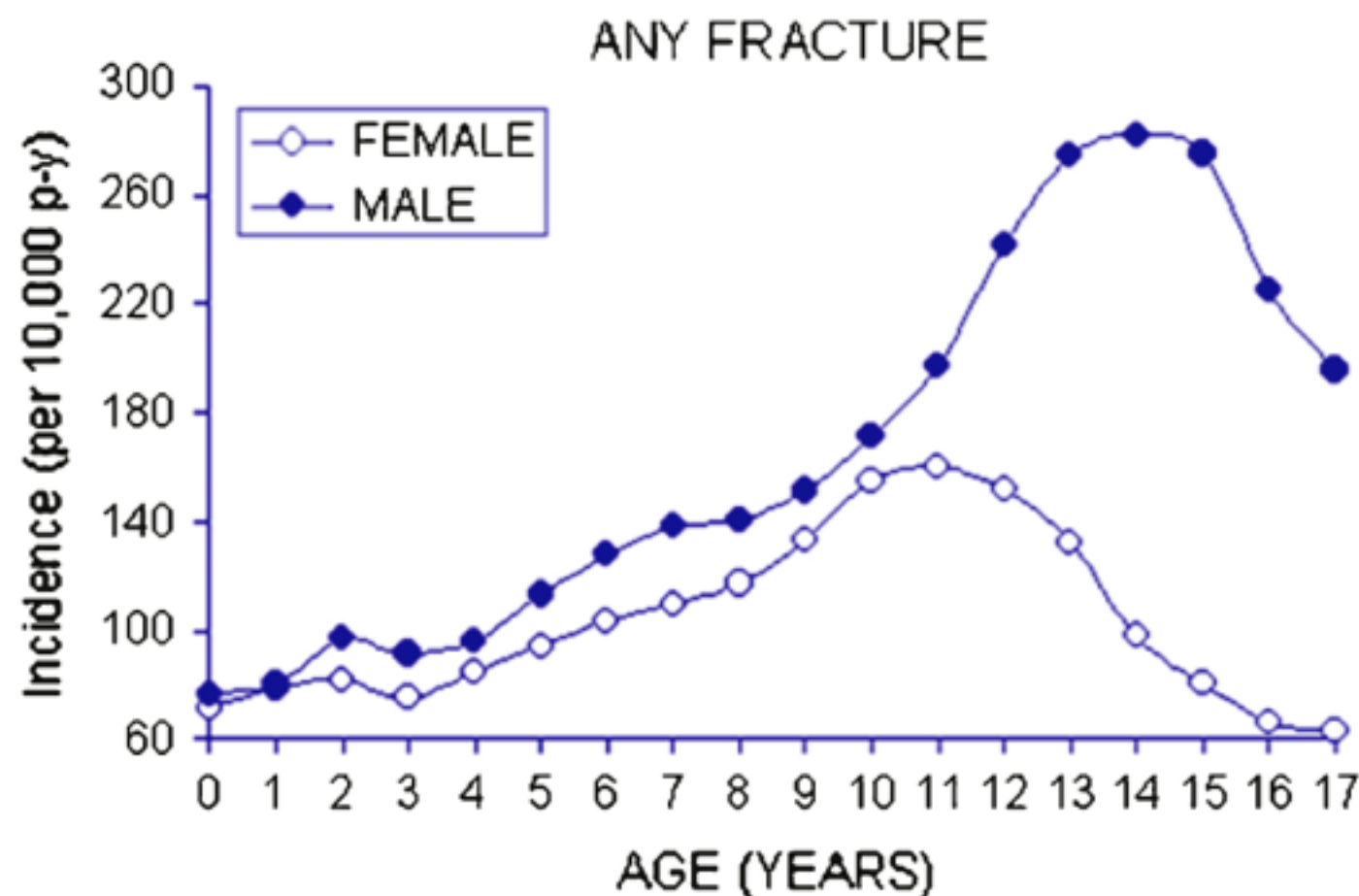
Figure 1. Incidence of fractures among children from the General Practice Research Database (GPRD). Reproduced from Cooper et al (2004, *Journal of Bone and Mineral Research* **19:** 1976–1981) with permission.

Cooper et al (2004, *Journal of Bone and Mineral Research* **19:** 1976–1981)

ELSEVIER

Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 22, No. 5, pp. 687–700, 2008
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available online at http://www.sciencedirect.com

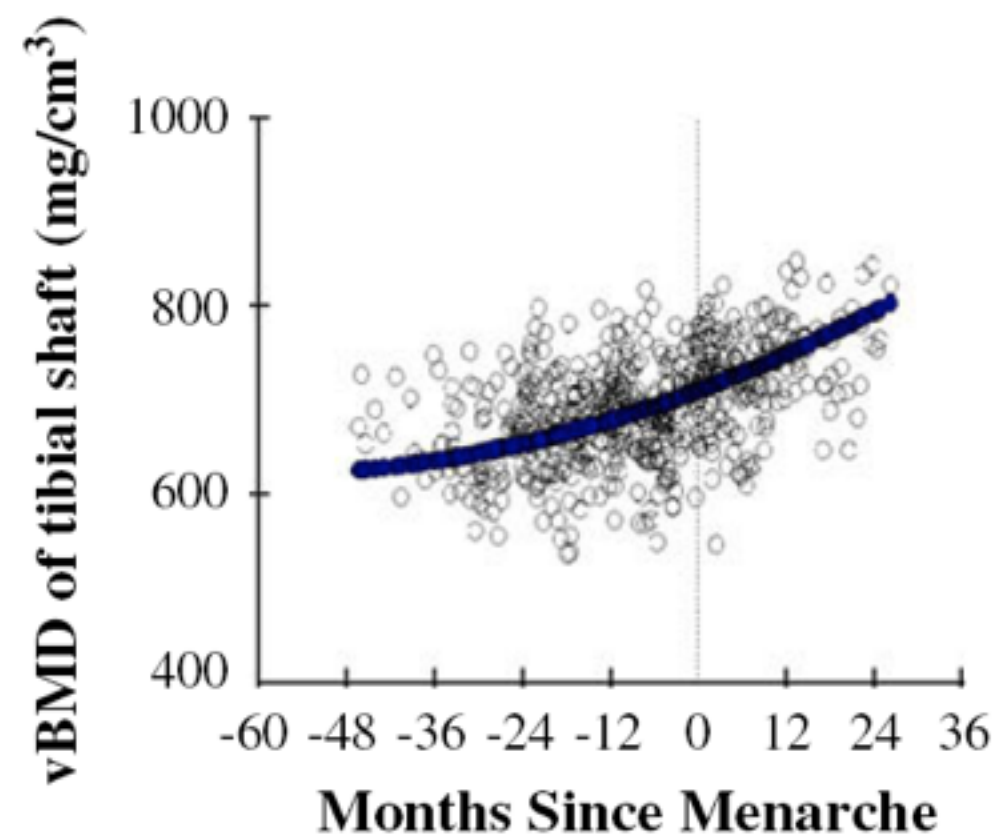
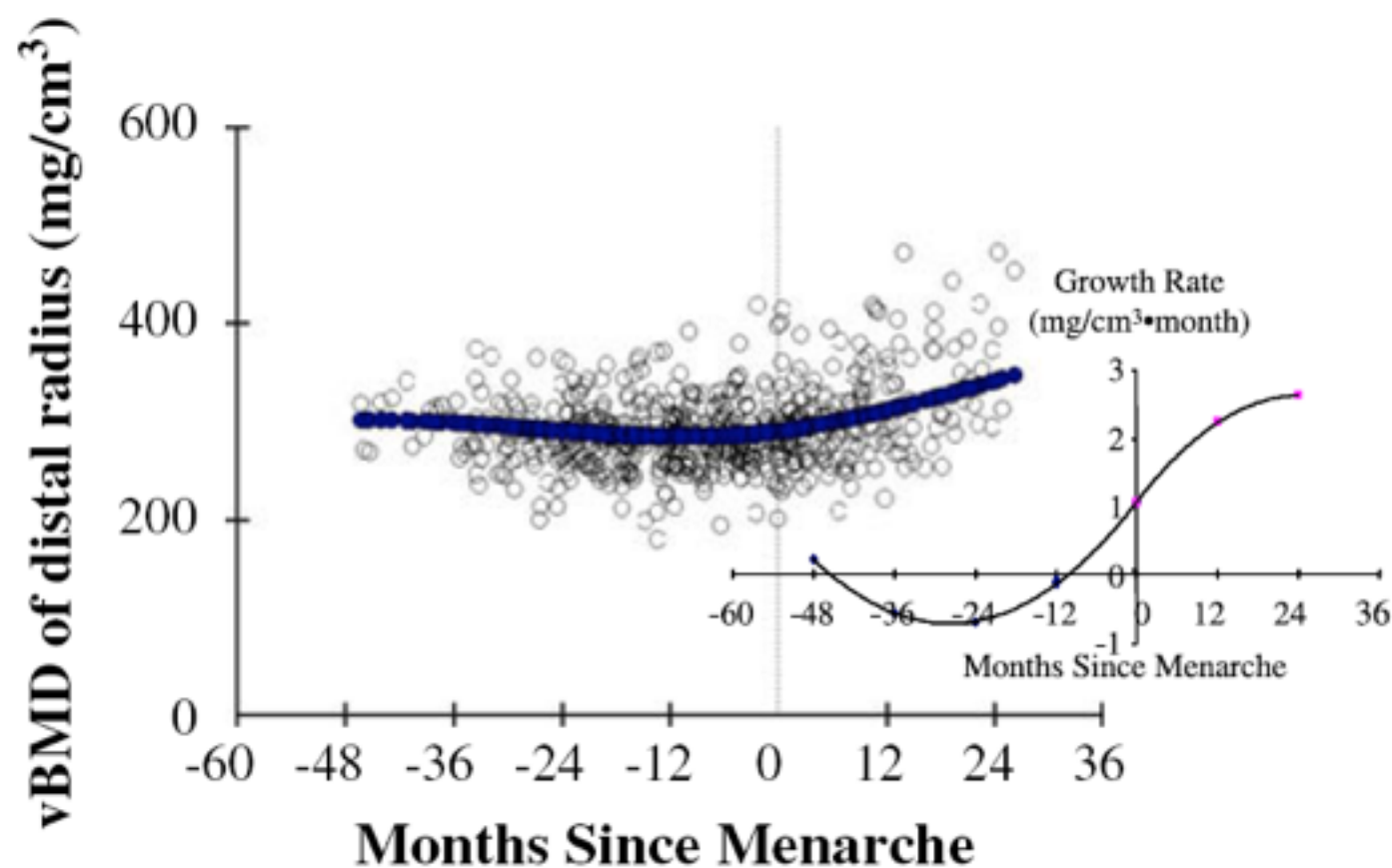
BEST PRACTICE & RESEARCH

2

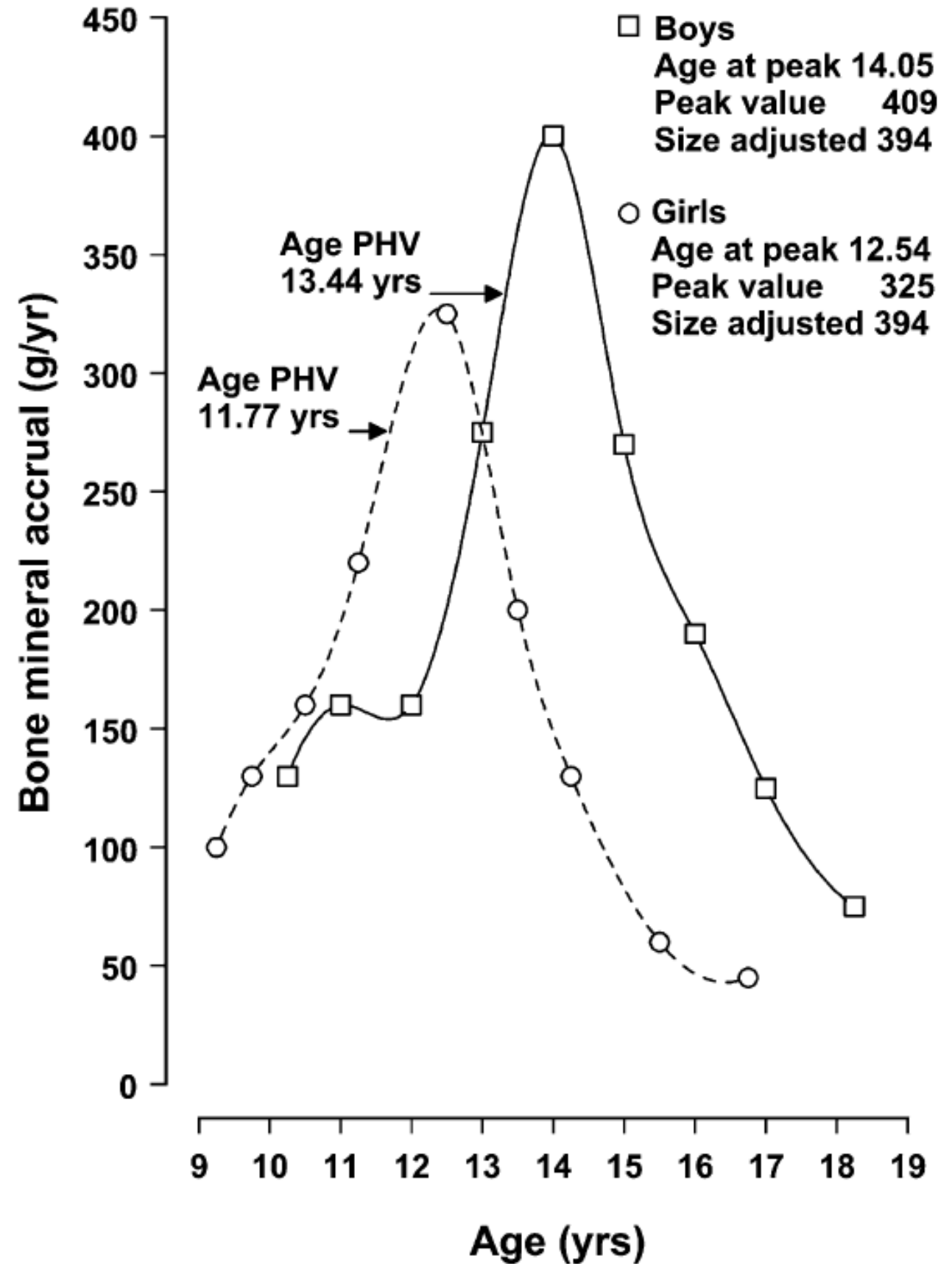
Skeletal growth and peak bone strength

Qingju Wang* MD, PhD
Research Fellow
Endocrine Centre, Centaur Building, Heidelberg Repatriation Hospital/Austin Health, Heidelberg, VIC 3081, Australia

Ego Seeman BSc, MBBS, MD, FRACP
Professor of Medicine
Department of Endocrinology and Medicine, Austin Health, University of Melbourne, Melbourne, Australia

Osteoporos Int (2006) 17: 337–347
DOI 10.1007/s00198-005-2039-5

REVIEW

Review: developmental origins of osteoporotic fracture

Cyrus Cooper · Sarah Westlake · Nicholas Harvey
Kassim Javaid · Elaine Dennison · Mark Hanson

- Forearm and upper arm fractures are frequent in childhood and adolescence
- During pubertal growth spurt, bone longitudinal growth and mineralization are dissociated temporarly; thus, there is a temporary bone fragility.

Fractures during Childhood and Adolescence in Healthy Boys: Relation with Bone Mass, Microstructure, and Strength

T. Chevalley, J. P. Bonjour, B. van Rietbergen, S. Ferrari, and R. Rizzoli

Division of Bone Diseases (T.C., J.P.B., S.F., R.R.), University Hospitals and Faculty of Medicine, CH-1211 Geneva 14, Switzerland; and Department of Biomedical Engineering (B.v.R.), Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands

J Clin Endocrinol Metab, October 2011, 96(10):3134–3142

TABLE 2. Characteristics of boys at 7.4 and 15.2 yr according to their fracture history at 15.2 yr

	Without fracture, n = 89	With fracture, n = 87	*P*	*P*[a]	Without fracture, n = 89	With fracture, n = 87	*P*	*P*[b]
Age (yr)	7.4 ± 0.4	7.4 ± 0.4			15.2 ± 0.5	15.2 ± 0.5		
Pubertal stage (n)[c]	All P1	All P1			P2 (1), P3 (7) P4 (49), P5 (32)	P2 (4), P3 (6) P4 (44), P5 (33)		
Height (cm)	126.1 ± 6.5	124.9 ± 5.7	0.173		172.2 ± 10.5	171.2 ± 8.8	0.484	
Weight (kg)	25.5 ± 5.0	25.0 ± 5.0	0.520		61.0 ± 13.0	59.4 ± 13.4	0.441	
BMI (kg/m^2)	15.9 ± 1.9	15.9 ± 2.1	0.884		20.5 ± 3.6	20.2 ± 3.6	0.579	
Calcium (mg/d)	767 ± 279	730 ± 250	0.359		1027 ± 526	1032 ± 554	0.949	
Total proteins (g/d)	48.5 ± 13.3	45.2 ± 11.1	0.082		65.4 ± 24.1	61.2 ± 23.1	0.241	
Total PA (kcal/d)	233 ± 96	249 ± 89	0.251		735 ± 449	705 ± 310	0.609	
Radial metaphysis BMD (mg/cm^2)	301 ± 28	290 ± 31	0.014	0.013	383 ± 54	379 ± 56	0.626	0.444
Radial diaphysis BMD (mg/cm^2)	481 ± 38	466 ± 37	0.010	0.034	660 ± 67	654 ± 70	0.583	0.716
Femoral neck BMD (mg/cm^2)	688 ± 70	663 ± 72	0.023	0.033	901 ± 133	847 ± 116	0.005	0.001
Total hip BMD (mg/cm^2)	690 ± 67	665 ± 72	0.017	0.032	992 ± 139	936 ± 133	0.007	0.002
Femoral diaphysis BMD (mg/cm^2)	1014 ± 85	982 ± 85	0.014	0.024	1682 ± 171	1623 ± 171	0.025	0.006
L2–L4 BMD (mg/cm^2)	568 ± 52	546 ± 57	0.010	0.017	918 ± 135	875 ± 133	0.032	0.010

All values are mean ± SD. BMI, Body mass index.

[a] *P* value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, and physical activity.

[b] *P* value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

[c] Pubertal maturity, with the number of boys at the corresponding Tanner stage shown within *parentheses*.

Fractures during Childhood and Adolescence in Healthy Boys: Relation with Bone Mass, Microstructure, and Strength

T. Chevalley, J. P. Bonjour, B. van Rietbergen, S. Ferrari, and R. Rizzoli

Division of Bone Diseases (T.C., J.P.B., S.F., R.R.), University Hospitals and Faculty of Medicine, CH-1211 Geneva 14, Switzerland; and Department of Biomedical Engineering (B.v.R.), Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands

J Clin Endocrinol Metab, October 2011, 96(10):3134–3142

TABLE 3. Microstructure and FEA of distal tibia and distal radius in 15.2-yr-old boys according to their fracture history

	Distal tibia				Distal radius		
	Without fracture, n = 89	With fracture, n = 87	*P*	*P*[a]	Without fracture, n = 87	With fracture, n = 81	*P*
D tot (mg HA/cm^3)	272 ± 45	262 ± 44	0.125	0.038	257 ± 38	255 ± 44	0.830
D cort (mg HA/cm^3)	730 ± 56	735 ± 52	0.551	0.766	637 ± 73	642 ± 72	0.688
D trab (mg HA/cm^3)	205 ± 27	196 ± 27	0.029	0.012	195 ± 27	192 ± 34	0.542
BV/TV (%)	17.1 ± 2.3	16.3 ± 2.2	0.030	0.012	16.2 ± 2.3	16.0 ± 2.8	0.544
Tb.N (mm^{-1})	2.13 ± 0.31	2.04 ± 0.26	0.040	0.036	2.23 ± 0.20	2.20 ± 0.21	0.351
Tb.Th (μm)	81.1 ± 10.6	80.8 ± 10.7	0.875	0.252	72.6 ± 8.4	72.4 ± 10.9	0.872
Tb.Sp (μm)	398 ± 62	418 ± 60	0.028	0.020	379 ± 41	387 ± 53	0.404
Ct.Th (μm)	851 ± 336	807 ± 293	0.464	0.332	388 ± 219	383 ± 209	0.890
CSA (mm^2)	888 ± 151	858 ± 132	0.167	0.400	333 ± 61	322 ± 56	0.209
Stiffness (kN/mm)	259.6 ± 54.7	244.6 ± 48.6	0.060	0.024	87.2 ± 21.6	83.5 ± 19.3	0.249
Estimated failure load (N)	12430 ± 2559	11706 ± 2235	0.050	0.016	4239 ± 996	4044 ± 894	0.189

All values are mean ± SD. D tot, D cort, and D trab, total, cortical, and trabecular volumetric density, respectively, expressed in milligrams of hydroxyapatite (HA); Tb.N, Tb.Th, and Tb.Sp, trabecular number, thickness, and spacing, respectively; Ct.Th, cortical thickness.

[a] *P* value after adjustment for age, height, weight, pubertal stage, calcium and protein intake, physical activity, and calcium supplement or placebo randomization between 7.4 and 8.4 yr.

2011 Chevalley Fractures

Bone Biopsy Findings and Correlation With Clinical, Radiological, and Biochemical Parameters in Children With Fractures

Mervi K Mäyränpää,[1] Inari S Tamminen,[2] Heikki Kröger,[2] and Outi Mäkitie[3]

[1]Department of Pediatric Surgery, Children's Hospital, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
[2]Department of Orthopaedics and Traumatology, Bone and Cartilage Research Unit, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland
[3]Department of Pediatrics, Children's Hospital, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland

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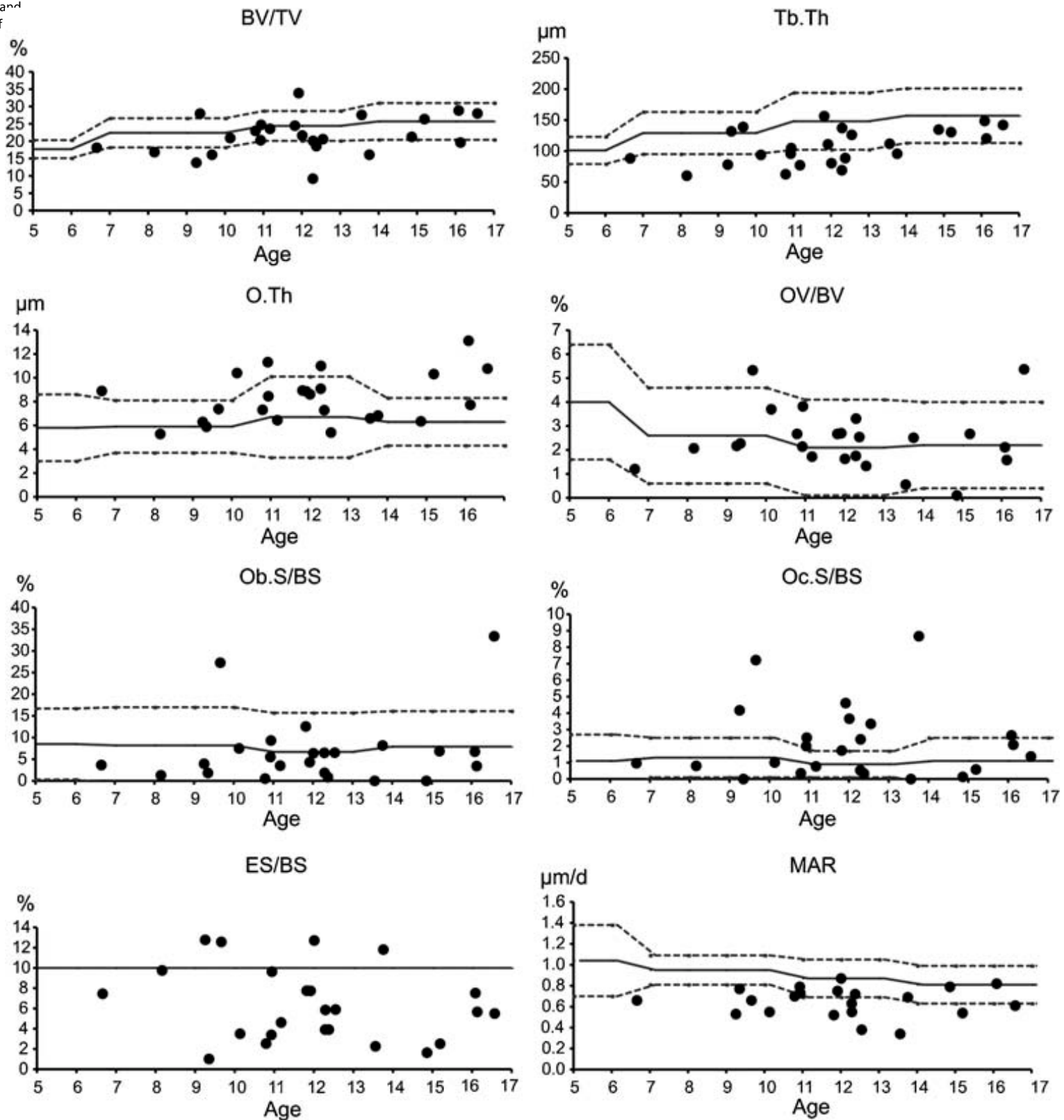
Fig. 1. Individual histomorphometric results of all 24 fracture-prone children. Lines represent age-specific reference values (from Glorieux et al.(13)): mean ` 2SD, except for BV/TV (mean ` 1SD), and for ES/BS (10%). Age in years.

Fractures

- The clinical challenge lies in the early discrimination of those children with skeletal pathology leading to fracture
- Hip and vertebral fractures are rare in pediatrics. Also, fractures that take place after minimal trauma may be concerning.
- Taken together, a history of axial skeletal fractures or multiple fractures from low biomechanical force may be indicators of skeletal fragility and should raise concern for osteoporosis in children.

Pediatric Rheumatology

Review

Open Access

Osteoporosis in children: pediatric and pediatric rheumatology perspective: a review

Yosef Uziel*[1,2], Eyal Zifman[1,2] and Philip J Hashkes[3]

Address: [1]Pediatric Rheumatology Unit, Pediatric Department, Meir Medical Center, Kfar Saba, Israel, [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel and [3]Section of Pediatric Rheumatology, Dept of Rheumatic Diseases, Cleveland Clinic Foundation, Cleveland OH, USA

Email: Yosef Uziel* - uziely@zahav.net.il; Eyal Zifman - ezifman@gmail.com; Philip J Hashkes - hashkep@ccf.org

* Corresponding author

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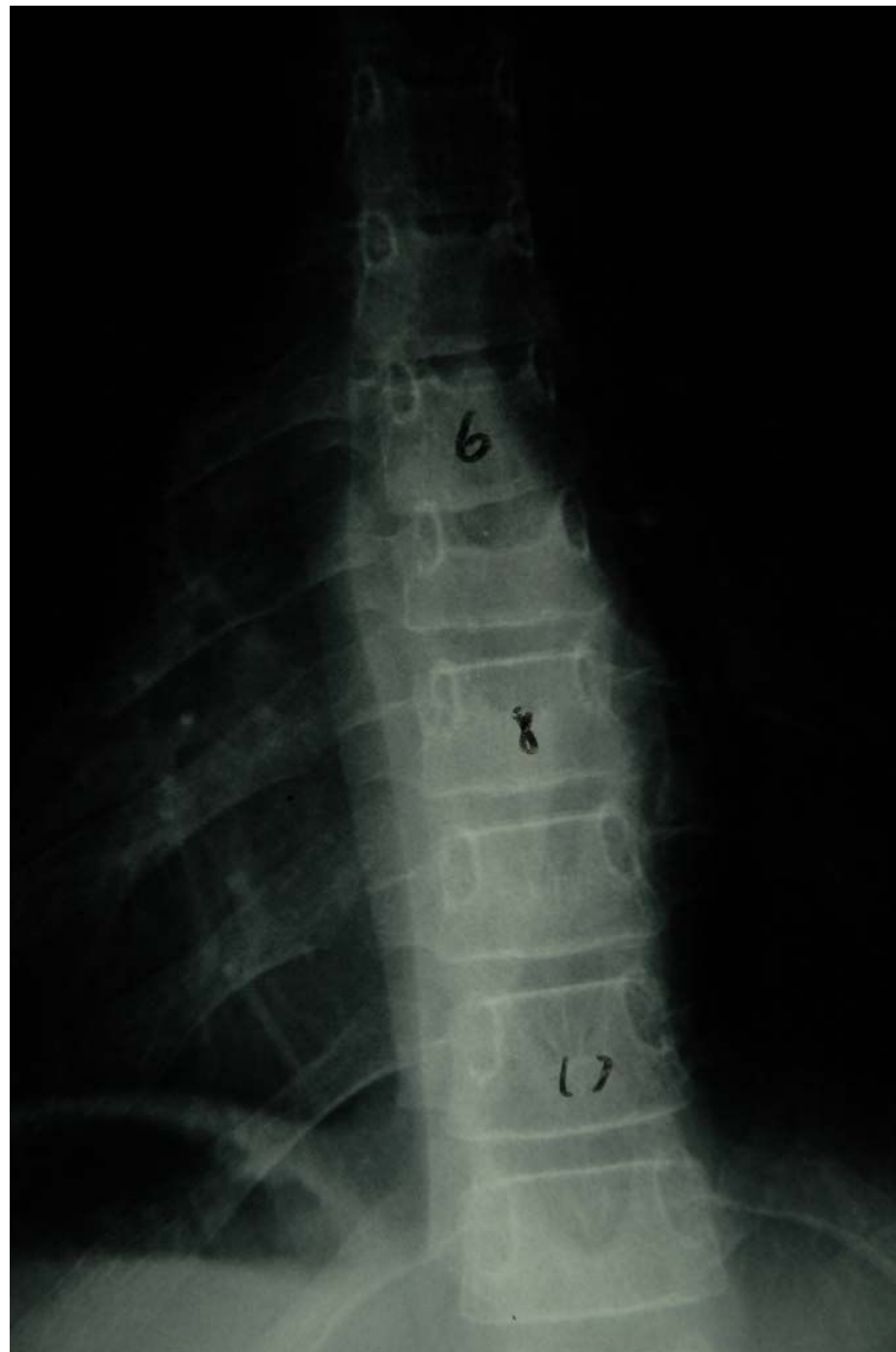


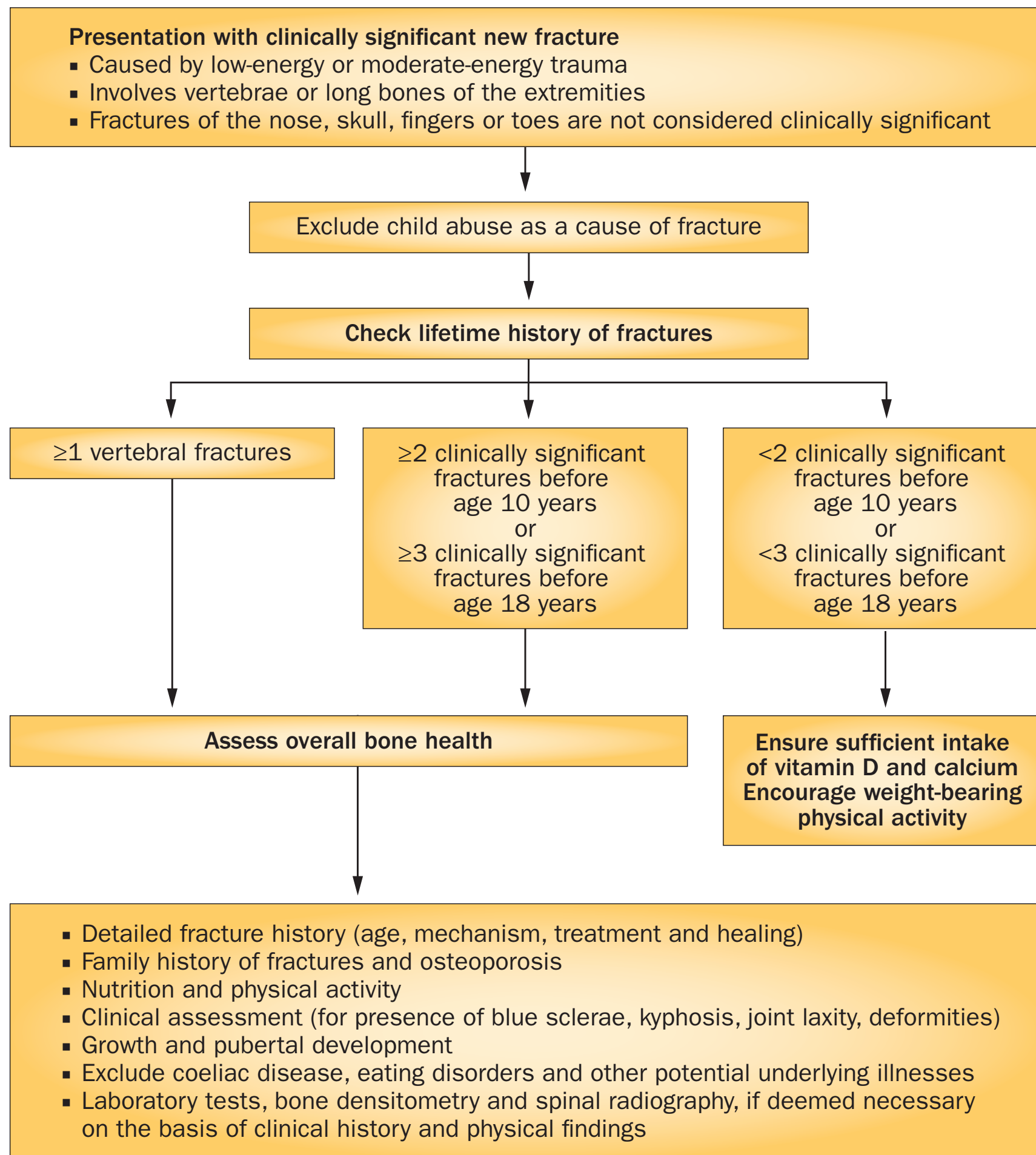
Figure 1
Spine radiograph demonstrating an osteoporosis-related T7 vertebral fracture.

2009 Uziel osteop in child

Causes, mechanisms and management of paediatric osteoporosis

Outi Mäkitie

NATURE REVIEWS | RHEUMATOLOGY

Figure 1 An algorithm for assessment of an otherwise healthy child who presents with a new fracture. In a hospital-based study of 1,412 children with a new fracture, use of these screening criteria identified 66 children (5%) as being fracture-prone. In this group, several children had asymptomatic vertebral compressions and a high number of children had vitamin D deficiency, inadequate calcium intake, or insufficient physical activity.

Fractures in children and adolescents

Paediatric patients with a suspected osteoporotic fracture should have:

a thorough assessment of diet and other lifestyle factors

DXA bone densitometry scanning

spinal radiography (*)

assessment of endocrine and vitamin D status

examination of calcium homeostasis and urine calcium and phosphate excretion

Fractures in children and adolescents

- Bone turnover markers are of little value for diagnostic purposes but can be used in monitoring treatment response.

  For children with an underlying chronic illness, bone health screening should be targeted to high-risk populations, based on clinical suspicion and individualized evaluation.

  Spinal compression fractures are prevalent but usually asymptomatic in children with chronic illness

  Histomorphometry of transiliac bone biopsy samples can provide valuable information about bone quality and turnover. It should be reserved only for research and unusually complicated situations.

Fractures in children and adolescents

Prospective studies have shown that low BMD in childhood is associated with increased future fracture risk, that children with fractures have lower bone mass for their body size than children without fractures, and that (at least in male individuals) a childhood fracture is predictive of low BMD and reduced bone size in young adulthood.

Despite these observations, the fracture risk associated with low bone mass, low BMD or a positive fracture history in an individual child remains largely unknown.

Osteoporosis in children and adolescents

- Osteoporosis in an otherwise healthy child is defined as primary
- Osteoporosis caused by an underlying illness and/or its treatment is defined as secondary

Diagnosi e terapia dell'osteoporosi in età evolutiva

Tabella 2. Classificazione dell'osteoporosi in età evolutiva

	Idiopatica	Osteoporosi idiopatica giovanile
Primaria	Malattie ereditabili del tessuto connettivo	• Osteogenesi imperfetta • Sindrome di Ehler-Danlos • Sindrome di Bruck • Sindrome di Marfan • Sindrome osteoporosi-pseudoglioma • Omocistinuria
Secondaria	Malattie neuromuscolari con diminuzione della mobilità	• Paralisi cerebrale • Distrofia muscolare di Duchenne • Immobilizzazione prolungata • Spina bifida • Atrofia muscolare spinale
	Malattie croniche	• Leucemia • Malattie del connettivo • Fibrosi cistica • Dermatomiosite • Morbo celiaco • Morbo di Crohn • Talassemia • Lupus eritematoso sistemico • Artrite giovanile idiopatica • Cirrosi biliare primitiva • Sindrome nefrosica • Anoressia nervosa • Infezione da HIV • Trapianti d'organo
	Malattie endocrine	• Ipogonadismo • Sindrome di Turner • Sindrome di Klinefelter • Deficit di GH • Ipertiroidismo • Diabete mellito giovanile *(non correttamente gestito)* • Sindrome di Cushing • Iperprolattinemia
	Malattie metaboliche congenite	• Intolleranza alle proteine • Glicogenosi • Malattia di Gaucher • Galattosemia
	Farmaci e interventi terapeutici	• Glucocorticoidi • Ciclosporina • Metotrexate • Eparina • Anticonvulsivanti • Radioterapia

Antoniazzi F.
Informer in Endocrinologia, 2010; 13: 6-13

Diagnosi e terapia dell'**osteoporosi**
in **età evolutiva**

Tabella 3. **Metodi d'indagine della massa ossea in età evolutiva**

Metodo	Sede di misura
Dual energy X-ray absorptiometry - DXA	Vertebre lombari, collo femorale, radio, total body
Tomografia computerizzata quantitativa periferica - pQCT	Radio-ulna, tibia
Ultrasonografia quantitativa - QUS	Falangi della mano, calcagno, tibia

Antoniazzi F.
Informer in Endocrinologia, 2010; 13: 6-13

CARATTERISTICHE DELLE PRINCIPALI TECNICHE DENSITOMETRICHE PER L'UTILIZZO IN ETÀ EVOLUTIVA

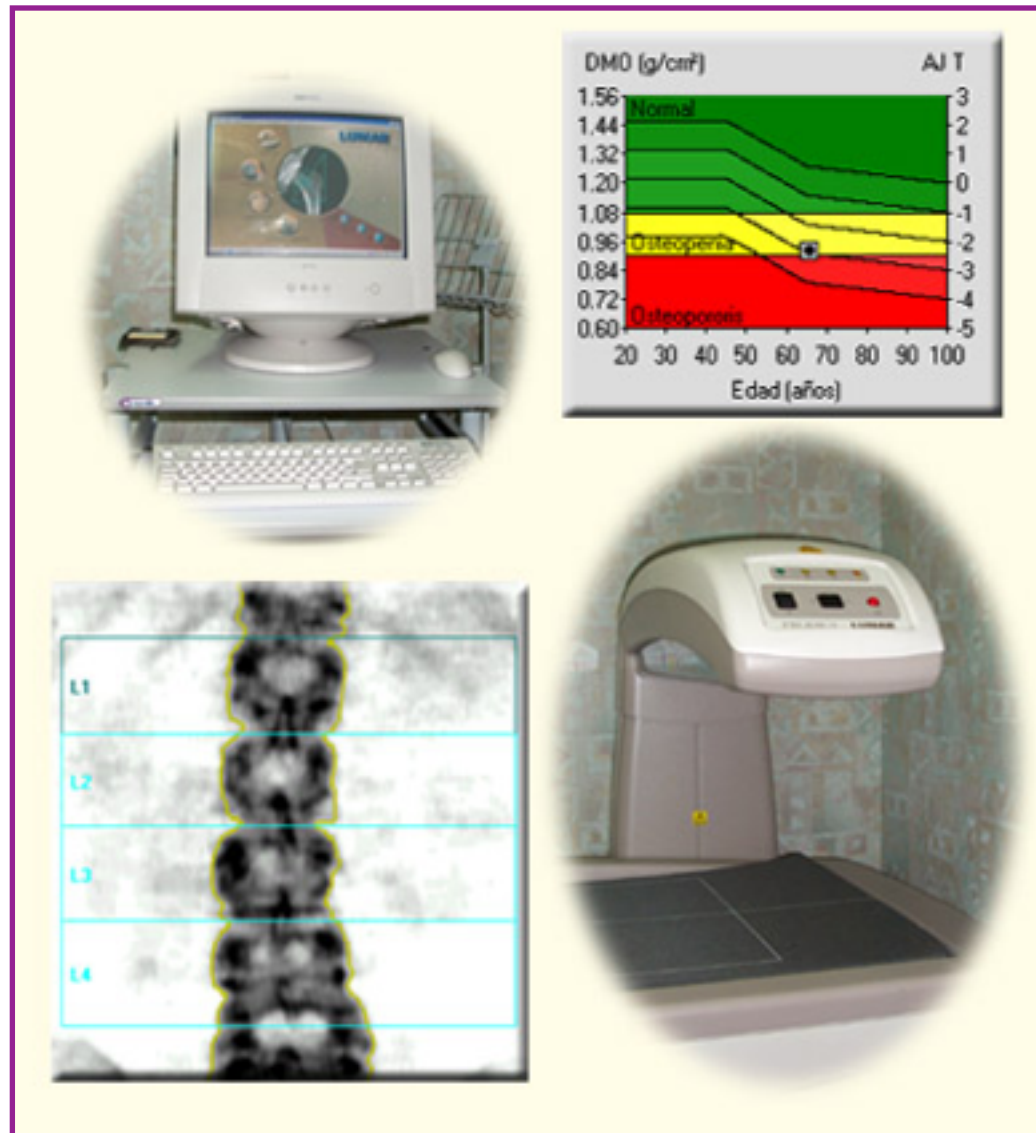
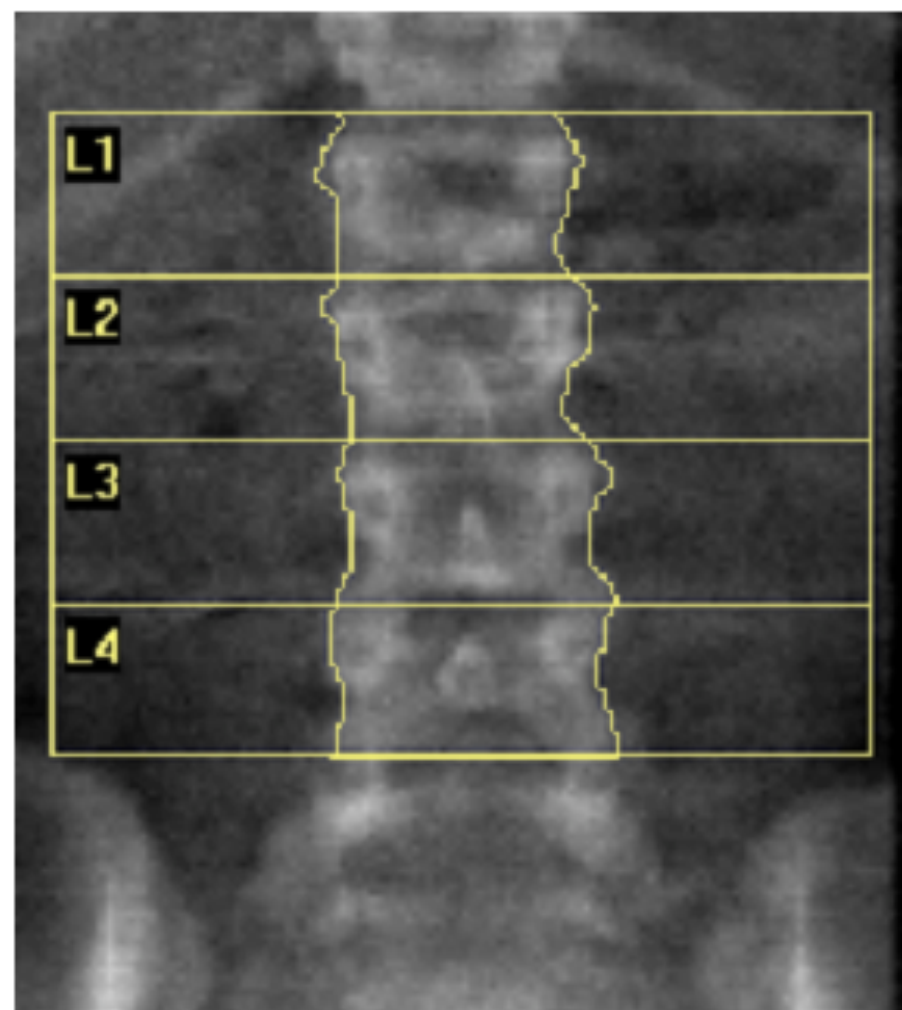
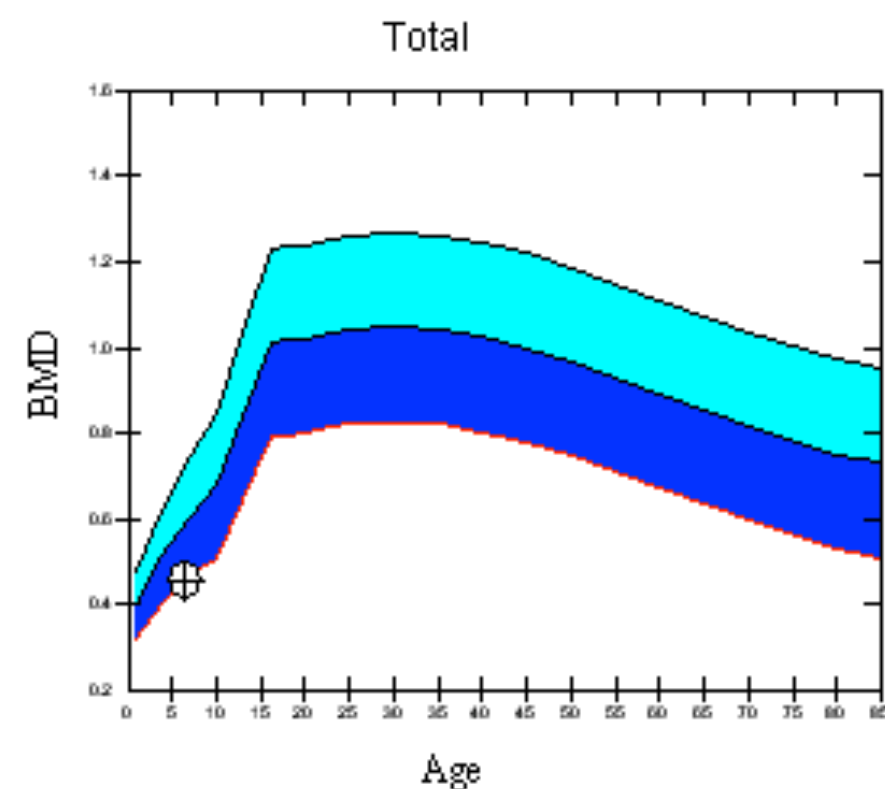
Tecnica	Sito di misurazione	Componente ossea misurata	Precisione, %	Accuratezza, %	ED, µSv	Durata esame,min
Doppio raggio-x* (DXA)	vertebre lombari, collo femore, radio, corpo *in toto*	corticale e trabecolare integrata	0.7 – 2.6	4 - 7	0.02 - 4.6°	2 - 15°
Tomografia computerizzata quantitativa periferica (pQCT)	radio/ulna	corticale e trabecolare separate	1 - 3	5 - 14§	10	3 - 5
Ultrasonografia quantitativa (QUS)	falangi della mano, calcagno, tibia	corticale e trabecolare integrata	0.4 – 5.4	-	Nessuna	5

*Metodi "pencil beam". Per i metodi "fan beam" il tempo di scansione è di 10-30 sec. con ED (dose radiante effettiva) 6.7-57.0 µSv (2, 3, 38). °colonna lombare, femore e total body. §Limiti riferiti alla densità minerale ossea volumetrica corticale e trabecolare.

Tecniche di misurazione della massa ossea

Densitometria ossea DXA

Tecniche di misurazione della massa ossea

Densitometria ossea DXA

k = 1.144, d0 = 49.6
116 x 91

Scan Information:

Scan Date: 02 February 2011 ID: A02021105
Scan Type: x Lumbar Spine
Analysis: 02 February 2011 09:19 Version 12.4:3
Lumbar Spine (auto low density)
Model: Discovery A (S/N 81587)

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - Score	Z - Score
L1	7.73	2.84	0.368		
L2	7.86	3.69	0.469		
L3	8.32	3.89	0.468		
L4	8.50	4.41	0.520		
Total	**32.41**	**14.84**	**0.458**		**-2.0**

Total BMD CV 1.0%, ACF = 1.027, BCF = 1.003, TH = 5.385

Revised Reference Curves for Bone Mineral Content and Areal Bone Mineral Density According to Age and Sex for Black and Non-Black Children: Results of the Bone Mineral Density in Childhood Study

Babette S. Zemel, Heidi J. Kalkwarf, Vicente Gilsanz, Joan M. Lappe,
Sharon Oberfield, John A. Shepherd, Margaret M. Frederick, Xiangke Huang,
Ming Lu, Soroosh Mahboubi, Thomas Hangartner, and Karen K. Winer

J Clin Endocrinol Metab, October 2011, 96(10):3160–3169

TABLE 2. Age- and sex-specific reference percentiles for total body less head bone mineral content for non-Black children

	TBLH BMC (g)															
	Non-Black females								Non-Black males							
			M								M					
Age (yr)	L	S	3rd	10th	50th	90th	97th	HZ prediction equation	L	S	3rd	10th	50th	90th	97th	HZ prediction equation
5	−0.019	0.186	258	288	365	463	518	−0.051 + (HZ × 0.958)	−0.058	0.160	268	295	362	445	490	0.207 + (HZ × 0.941)
6	−0.019	0.166	344	380	470	581	643	0.134 + (HZ × 0.755)	−0.058	0.160	347	382	468	575	634	0.244 + (HZ × 0.546)
7	−0.019	0.152	422	463	562	683	749	0.181 + (HZ × 0.793)	−0.058	0.160	418	459	563	692	763	0.114 + (HZ × 0.716)
8	−0.019	0.146	483	527	635	766	837	0.182 + (HZ × 0.827)	−0.058	0.160	479	527	646	794	876	0.062 + (HZ × 0.775)
9	−0.019	0.146	537	586	706	851	929	0.127 + (HZ × 0.742)	−0.058	0.160	540	594	728	895	986	0.069 + (HZ × 0.756)
10	−0.019	0.152	598	656	797	968	1062	−0.024 + (HZ × 0.769)	−0.058	0.160	596	656	804	988	1089	−0.002 + (HZ × 0.823)
11	−0.019	0.169	674	745	926	1150	1274	−0.125 + (HZ × 0.765)	−0.058	0.160	664	730	895	1100	1213	−0.032 + (HZ × 0.885)
12	−0.019	0.185	777	868	1099	1393	1558	−0.103 + (HZ × 0.757)	−0.058	0.160	762	838	1028	1263	1393	−0.154 + (HZ × 0.961)
13	−0.019	0.182	914	1019	1286	1624	1812	−0.090 + (HZ × 0.740)	−0.058	0.160	898	988	1211	1489	1642	−0.220 + (HZ × 1.022)
14	−0.019	0.165	1049	1158	1431	1769	1954	−0.125 + (HZ × 0.693)	−0.058	0.160	1079	1186	1454	1788	1971	−0.219 + (HZ × 1.041)
15	−0.019	0.151	1149	1258	1526	1852	2028	−0.165 + (HZ × 0.701)	−0.058	0.160	1276	1403	1720	2114	2331	−0.201 + (HZ × 0.903)
16	−0.019	0.142	1212	1320	1582	1897	2067	−0.201 + (HZ × 0.753)	−0.058	0.160	1427	1568	1923	2364	2606	−0.185 + (HZ × 0.792)
17	−0.019	0.137	1247	1354	1612	1920	2085	−0.235 + (HZ × 0.758)	−0.058	0.160	1524	1676	2055	2525	2785	−0.164 + (HZ × 0.751)
18	−0.019	0.134	1263	1369	1625	1930	2093	−0.226 + (HZ × 0.785)	−0.058	0.160	1577	1734	2127	2614	2882	−0.195 + (HZ × 0.741)
19	−0.019	0.134	1267	1372	1628	1932	2094	−0.235 + (HZ × 0.829)	−0.058	0.160	1605	1764	2163	2659	2932	−0.190 + (HZ × 0.739)
20	−0.019	0.133	1268	1374	1629	1933	2095	−0.218 + (HZ × 0.774)	−0.058	0.160	1624	1785	2189	2690	2967	−0.195 + (HZ × 0.727)

L, M, and S values to calculate Z-scores and HZ prediction equations to calculate height adjusted Z-scores are also shown. This measure excludes the BMC of the head from the total body measurement. HZ, Ht-Z.

Revised Reference Curves for Bone Mineral Content and Areal Bone Mineral Density According to Age and Sex for Black and Non-Black Children: Results of the Bone Mineral Density in Childhood Study

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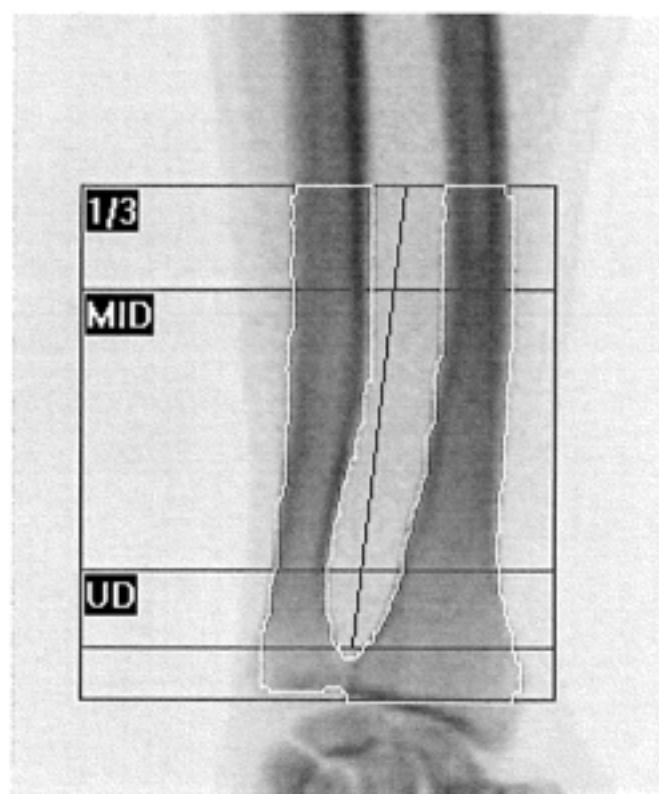
J Clin Endocrinol Metab, October 2011, 96(10):3160–3169

TABLE 4. Age- and sex-specific reference percentiles for lumbar spine aBMD for non-Black children

Lumbar spine aBMD																
	Non-Black females								Non-Black males							
			M								M					
Age (yr)	L	S	3rd	10th	50th	90th	97th	HZ prediction equation	L	S	3rd	10th	50th	90th	97th	HZ prediction equation
5	−0.206	0.115	0.405	0.433	0.501	0.582	0.625	−0.385 + (HZ × 0.430)	0.436	0.121	0.380	0.412	0.483	0.562	0.601	−0.129 + (HZ × 0.396)
6	−0.178	0.117	0.417	0.447	0.518	0.604	0.649	−0.156 + (HZ × 0.427)	0.436	0.121	0.399	0.432	0.507	0.589	0.630	−0.077 + (HZ × 0.411)
7	−0.150	0.120	0.429	0.461	0.536	0.626	0.674	−0.007 + (HZ × 0.473)	0.436	0.121	0.417	0.451	0.530	0.616	0.658	−0.057 + (HZ × 0.455)
8	−0.120	0.122	0.442	0.475	0.555	0.650	0.701	0.041 + (HZ × 0.522)	0.436	0.121	0.434	0.470	0.552	0.641	0.685	−0.037 + (HZ × 0.469)
9	−0.080	0.126	0.457	0.493	0.578	0.680	0.734	0.034 + (HZ × 0.501)	0.436	0.121	0.450	0.488	0.572	0.665	0.711	−0.005 + (HZ × 0.510)
10	−0.022	0.131	0.479	0.518	0.612	0.725	0.785	−0.035 + (HZ × 0.485)	0.436	0.121	0.467	0.506	0.594	0.690	0.737	−0.005 + (HZ × 0.507)
11	0.061	0.139	0.510	0.555	0.664	0.792	0.861	−0.104 + (HZ × 0.542)	0.436	0.121	0.487	0.527	0.619	0.719	0.769	−0.039 + (HZ × 0.524)
12	0.169	0.145	0.560	0.613	0.740	0.888	0.966	−0.053 + (HZ × 0.593)	0.436	0.121	0.516	0.558	0.655	0.761	0.814	−0.100 + (HZ × 0.590)
13	0.286	0.140	0.631	0.690	0.829	0.988	1.069	−0.011 + (HZ × 0.592)	0.436	0.121	0.559	0.605	0.710	0.825	0.882	−0.151 + (HZ × 0.690)
14	0.392	0.128	0.703	0.764	0.904	1.059	1.137	−0.027 + (HZ × 0.539)	0.436	0.121	0.619	0.670	0.787	0.914	0.978	−0.099 + (HZ × 0.747)
15	0.473	0.116	0.757	0.817	0.954	1.101	1.174	−0.036 + (HZ × 0.553)	0.436	0.121	0.687	0.744	0.873	1.014	1.084	−0.071 + (HZ × 0.707)
16	0.527	0.108	0.794	0.853	0.984	1.125	1.195	−0.038 + (HZ × 0.595)	0.436	0.121	0.743	0.804	0.944	1.096	1.172	−0.032 + (HZ × 0.598)
17	0.560	0.103	0.817	0.874	1.003	1.140	1.206	−0.080 + (HZ × 0.589)	0.436	0.121	0.781	0.846	0.993	1.153	1.233	0.022 + (HZ × 0.565)
18	0.579	0.100	0.830	0.887	1.014	1.148	1.213	−0.080 + (HZ × 0.574)	0.436	0.121	0.805	0.872	1.023	1.189	1.271	−0.011 + (HZ × 0.601)
19	0.590	0.099	0.838	0.895	1.020	1.152	1.216	−0.083 + (HZ × 0.515)	0.436	0.121	0.821	0.889	1.043	1.212	1.296	−0.044 + (HZ × 0.617)
20	0.598	0.097	0.844	0.900	1.024	1.155	1.219	−0.091 + (HZ × 0.451)	0.436	0.121	0.833	0.902	1.059	1.230	1.316	−0.071 + (HZ × 0.587)

L, M, and S values to calculate Z-scores and HZ prediction equations to calculate height adjusted Z-scores are also shown. HZ, Ht-Z.

Name: Roscioli, Matteo	Sex: Male	Height: 172.0 cm
Patient ID:	Ethnicity: White	Weight: 70.0 kg
DOB: 16 May 1978		Age: 32

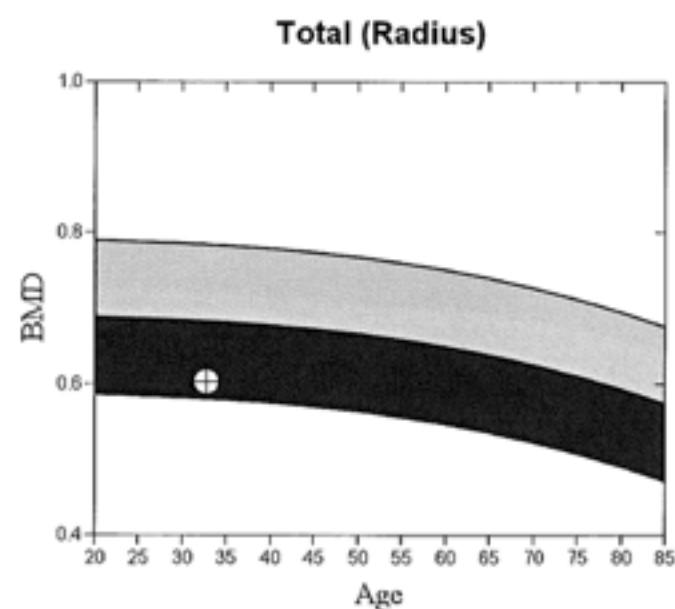
Referring Physician: AMBULATORIO

k = 1.200, d0 = 65.1
182 x 100, Forearm Length: 27.0 cm
DAP: 0.8 cGy*cm²

Scan Information:

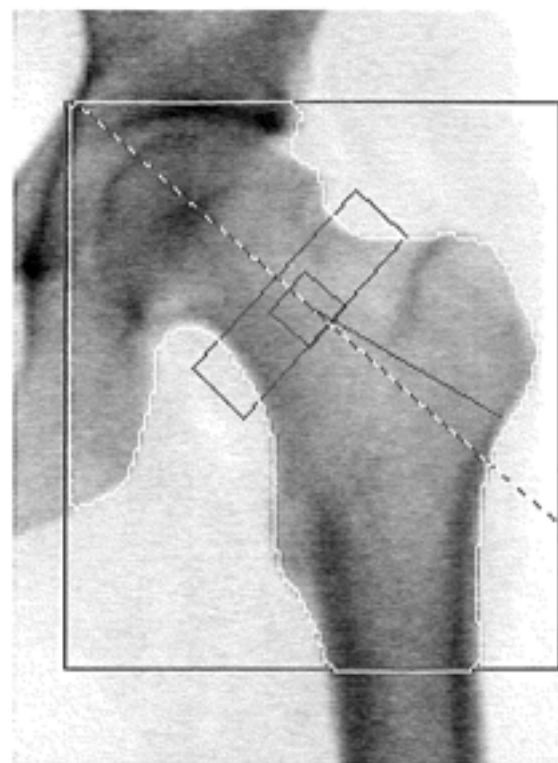
Scan Date: 04 March 2011 ID: A03041118
Scan Type: a R.Forearm
Analysis: 04 March 2011 11:49 Version 13.2:3
Right Forearm
Operator:
Model: QDR 4500A (S/N 45559)
Comment:

DXA Results Summary:

Radius	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
1/3	2.48	1.89	0.763	-1.0	93	-0.9	94
MID	7.06	4.52	0.641	-1.2	91	-1.1	91
UD	3.21	1.27	0.395	-2.6	72	-2.4	74
Total	**12.74**	**7.68**	**0.603**	**-1.6**	**88**	**-1.5**	**88**

Total BMD CV 1.0%, ACF = 1.028, BCF = 1.010
WHO Classification: Osteopenia
Fracture Risk: Increased

Comment:

Name: Roscioli, Matteo	Sex: Male	Height: 172.0 cm
Patient ID:	Ethnicity: White	Weight: 70.0 kg
DOB: 16 May 1978		Age: 32

Referring Physician: AMBULATORIO

k = 1.135, d0 = 50.0
98 x 113
NECK: 49 x 15
HAL: 107 mm
DAP: 3.5 cGy*cm²

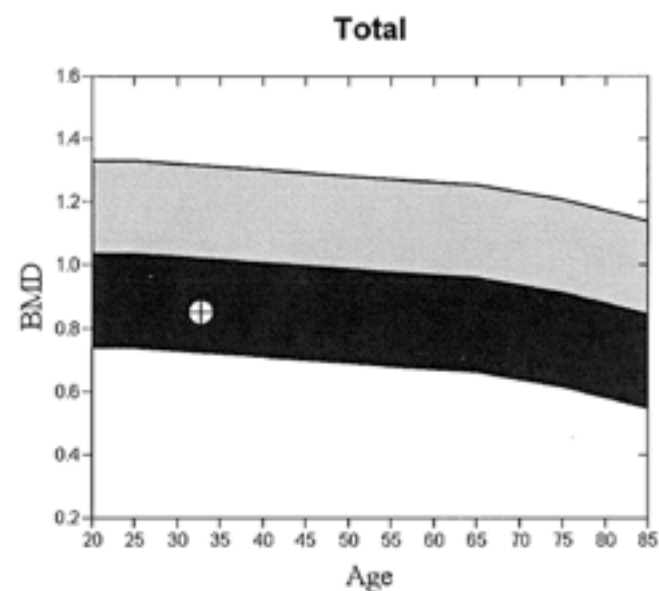
Scan Information:

Scan Date: 04 March 2011 ID: A03041117
Scan Type: a Left Hip
Analysis: 04 March 2011 11:49 Version 13.2:3
Hip
Operator:
Model: QDR 4500A (S/N 45559)
Comment:

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
Neck	5.35	3.56	0.665	-1.9	72	-1.7	74
Troch	10.13	5.69	0.562	-1.7	72	-1.6	74
Inter	23.19	23.61	1.018	-1.0	85	-0.9	86
Total	**38.67**	**32.87**	**0.850**	**-1.2**	**82**	**-1.1**	**83**
Ward's	1.30	0.78	0.598	-1.3	76	-0.9	82

Total BMD CV 1.0%, ACF = 1.028, BCF = 1.010, TH = 5.758
WHO Classification: Osteopenia

Total

BMD
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
20 25 30 35 40 45 50 55 60 65 70 75 80 85
Age

- La mancata considerazione degli effetti delle dimensioni ossee sulla stima dei valori di densità minerale ossea può determinare errori, anche rilevanti, nell'interpretazione dei risultati.

- Per ridurre l'interferenza delle dimensioni ossee sulla stima dei valori di densità minerale ossea misurati con la DXA sono stati proposti alcuni sistemi correttivi.

- Si può estrapolare la vBMD, normalizzando la aBMD per il volume della vertebra, assumendo che la vertebra sia un cubo oppure un cilindro

vBMD= aBMD x [4/(π x width)] [Kröger]

- Sono sempre delle forzature, in quanto le vertebre non possono definirsi figure geometriche perfette, come invece supposto dalle formule matematiche impiegate

IN VIVO EFFECT OF BONE SIZE ON BONE MINERAL PARAMETERS MEASURED BY DXA

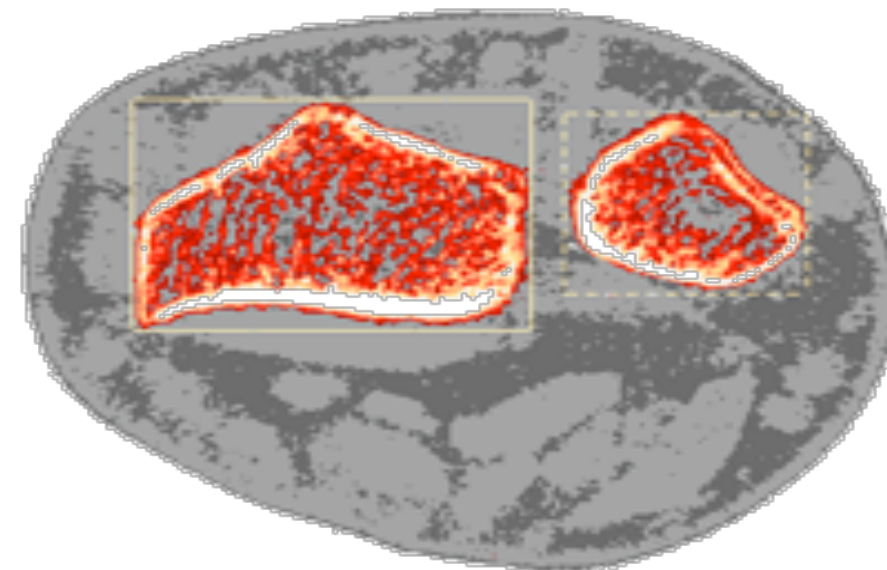
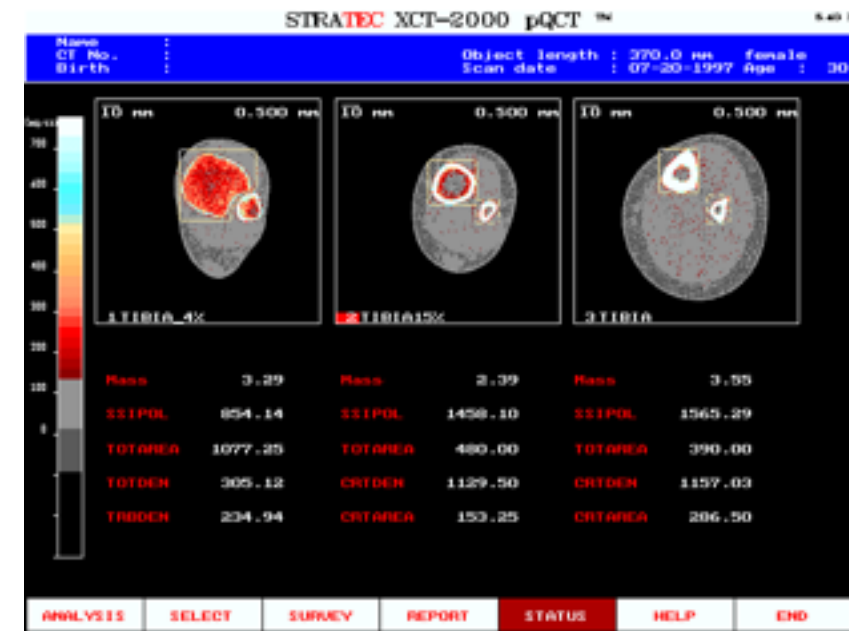
	Boy 1 (3° c)	Boy 2 (50° c)	Boy 3 (97° c)
Age, years	8.2	8.0	8.1
Height, cm	115	126	133
BMC, g	16.3	18.5	20.8
Bone area, cm^2	25.0	27.2	29.3
BMD, g/cm^2	0.652	0.680	0.710
Bone volume, cm^3	57.6	65.8	74.2
BMDvolume, g/cm^3	0.283	0.281	0.280

(Baroncelli GI et al. Horm Res 54, Suppl 1: 2, 2000)

Commento finale

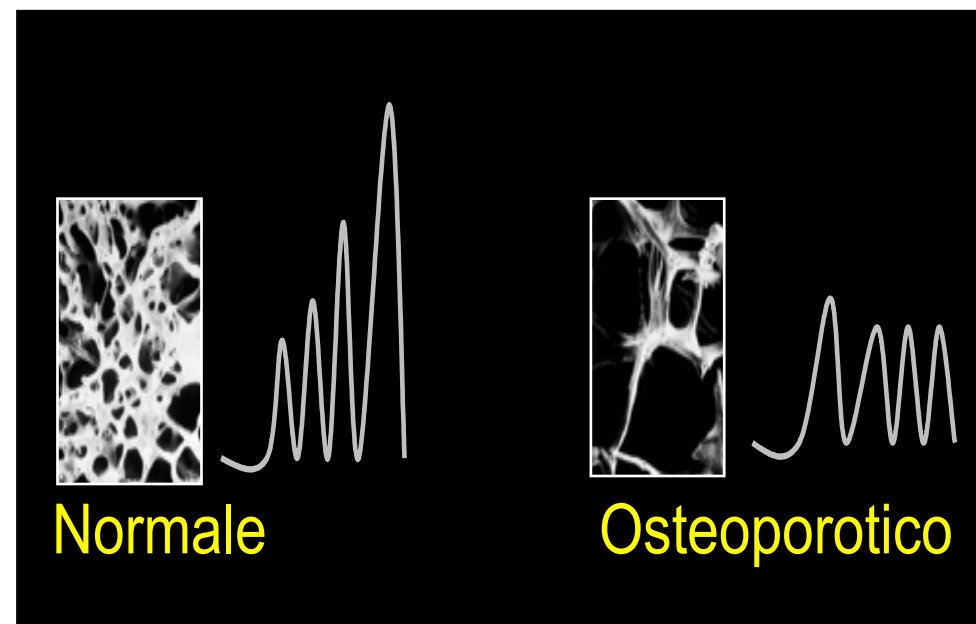
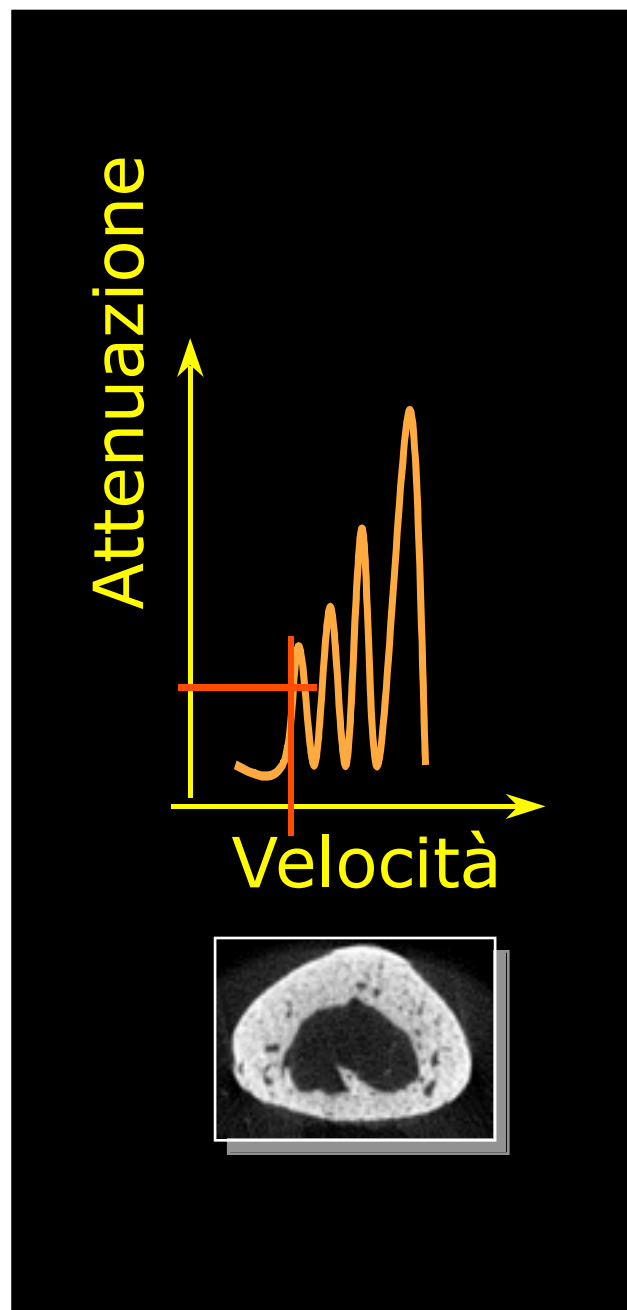
Lo studio dello stato osseo mediante DXA fornisce indicazioni riguardo alla massa di tessuto osseo ed alla sua mineralizzazione. Tali informazioni sono utili nel valutare il rischio di fratture.
Esse spiegano però solamente il 60-70% di tale rischio e quindi altri elementi, quali la geometria ossea e/o la qualità del tessuto osseo devono essere tenuti in giusta considerazione.

Tecniche di misurazione della massa ossea

Tomografia computerizzata periferica (pqct)

Ultrasonografia ossea

Ultrasonografia Ossea della Falangi

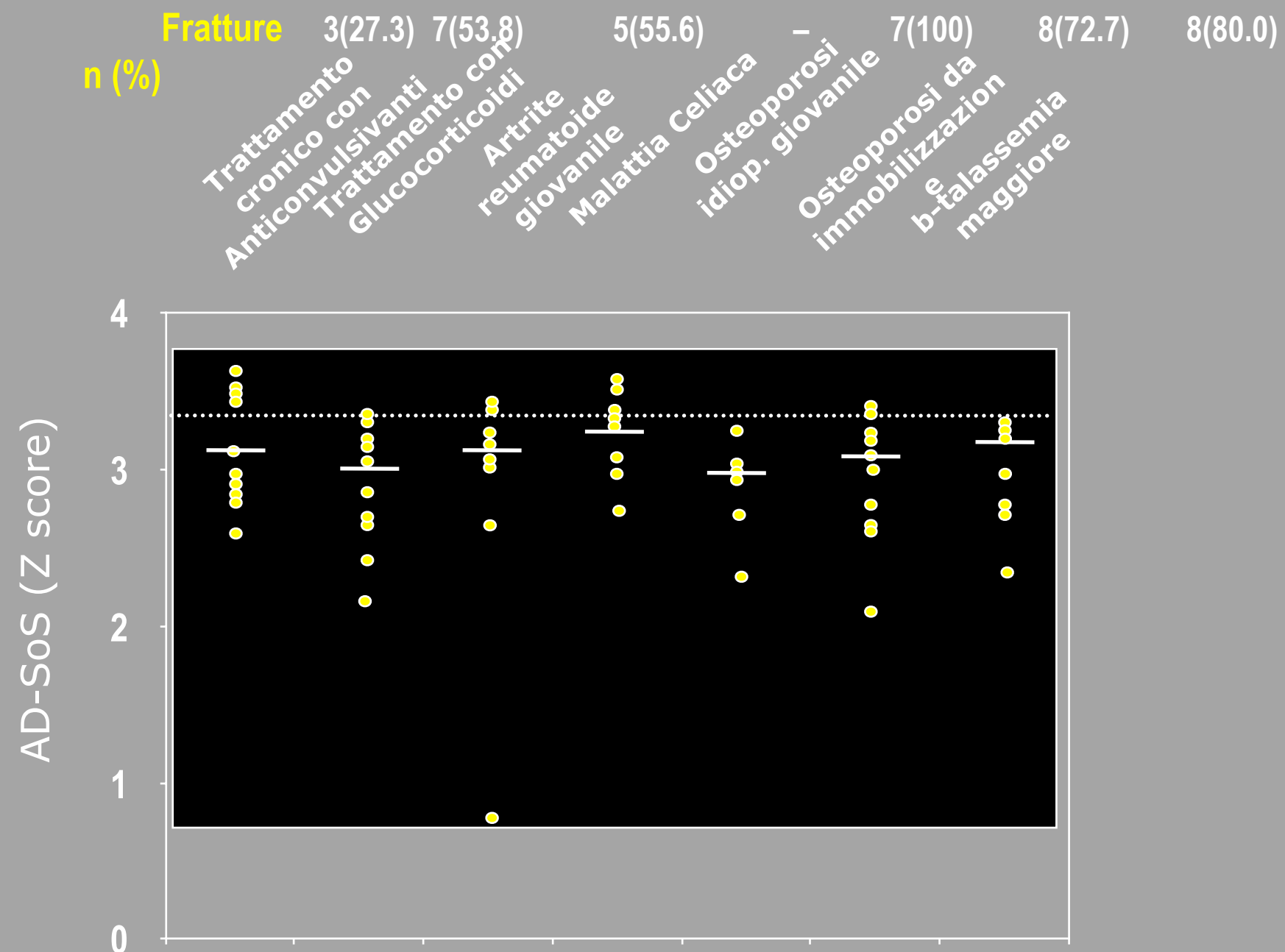
Ultrasonografia ossea

Le caratteristiche materiali e strutturali dell'osso influenzano velocità ed attenuazione degli ultrasuoni

Velocità (SOS)

Influenzata dalla densità minerale ossea e dalla elasticità

Attenuazione (BUA)

Perdita di energia dell'onda ultasonora, dovuta alla diffrazione, scattering e assorbimento durante l'attraversamento dei vari tessuti.
A livello osseo è in parte legata all'orientamento trabecolare.

Ultrasonografia ossea delle falangi

Ultrasonografia ossea

Utilizzo nei Neonati

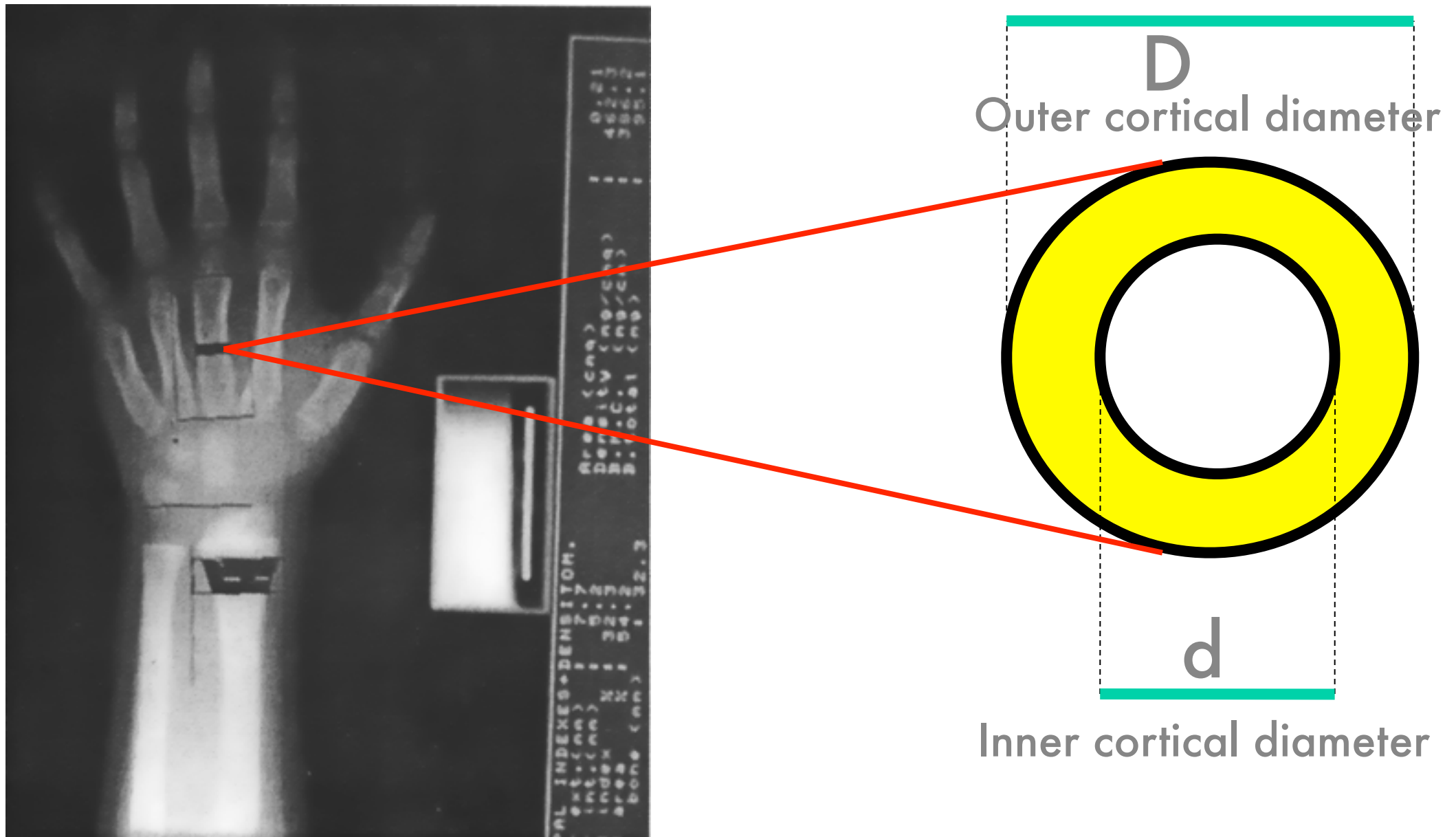



Figure 1. Site of examination

$$\text{Metacarpal Index} = (D-d)/D$$

$$\text{Medullary area} = (d/2) \times (d/2) \times 3.14$$

$$\text{Metacarpal Cortical Area} = (D/2) \times (D2) \times 3.14 - MA$$

$$\text{BBRI} = D^4-d^4/D$$ *(Bending Breaking Resistance Index)*

2.2 - Primary Osteoporosis

Causes, mechanisms and management of paediatric osteoporosis

Outi Mäkitie

NATURE REVIEWS | RHEUMATOLOGY

Table 1 Conditions associated with childhood-onset primary osteoporosis

Condition	Underlying genes	Disease mechanism	Mode of inheritance	Phenotype MIM number
Osteogenesis imperfecta (types I, II, III and IV)	*COL1A1, COL1A2*	Defect in type I collagen	AD	166200, 166210, 259420, 166220
Osteogenesis imperfecta (type V)	*IFITM5*	Dysregulation of bone formation	AD	610967
Osteogenesis imperfecta (type VI)	*SERPINF1*	Mineralization defect	AR	613982
Osteogenesis imperfecta (type VII)	*CRTAP*	Collagen prolyl 3-hydroxylation defect	AR	610682
Osteogenesis imperfecta (type VIII)	*LEPRE1*	Collagen prolyl 3-hydroxylation defect	AR	610915
Osteogenesis imperfecta (type IX)	*PPIB*	Collagen prolyl 3-hydroxylation defect	AR	259440
Osteogenesis imperfecta (type X)	*SERPINH1*	Chaperone defects	AR	613848
Osteogenesis imperfecta (type XI)	*FKBP10*	Chaperone defects	AR	610968
Osteogenesis imperfecta (type XII)	*SP7*	Impaired osteoblast differentiation	AR	613849
Osteogenesis imperfecta (type XIII)	*BMP1*	Defective collagen processing	AR	614856
Bruck syndrome	*PLOD2*	Impaired collagen cross-link formation	AR	609220
Osteoporosis–pseudoglioma syndrome	*LRP5*	Impaired Wnt signalling and osteoblast function	AR	259770
Ehlers–Danlos syndrome	*COL5A1, COL5A2, TNXB, COL3A1*	Defects in connective tissue	AD	130020 130050
Marfan syndrome	*FBN1, TGFBR2*	Defects in connective tissue	AD	154700
Cleidocranial dysplasia	*RUNX2*	Impaired bone formation	AD	119600
Calvarial doughnut lesions	Unknown	Unknown	AD	126550
Spondylo-ocular syndrome	Unknown	Unknown	AR	605822
Hajdu–Cheney syndrome	*NOTCH2*	Abnormal bone remodelling	AD	102500
Primary osteoporosis	*LRP5*	Impaired Wnt signalling and osteoblast function	AD	166710
Primary osteoporosis	*LRP6*	Impaired Wnt signalling and osteoblast function	AD	610947
Idiopathic juvenile osteoporosis	Unknown	Unknown	Unknown	259750

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MIM, Mendelian Inheritance in Man.

Osteogenesis Imperfecta

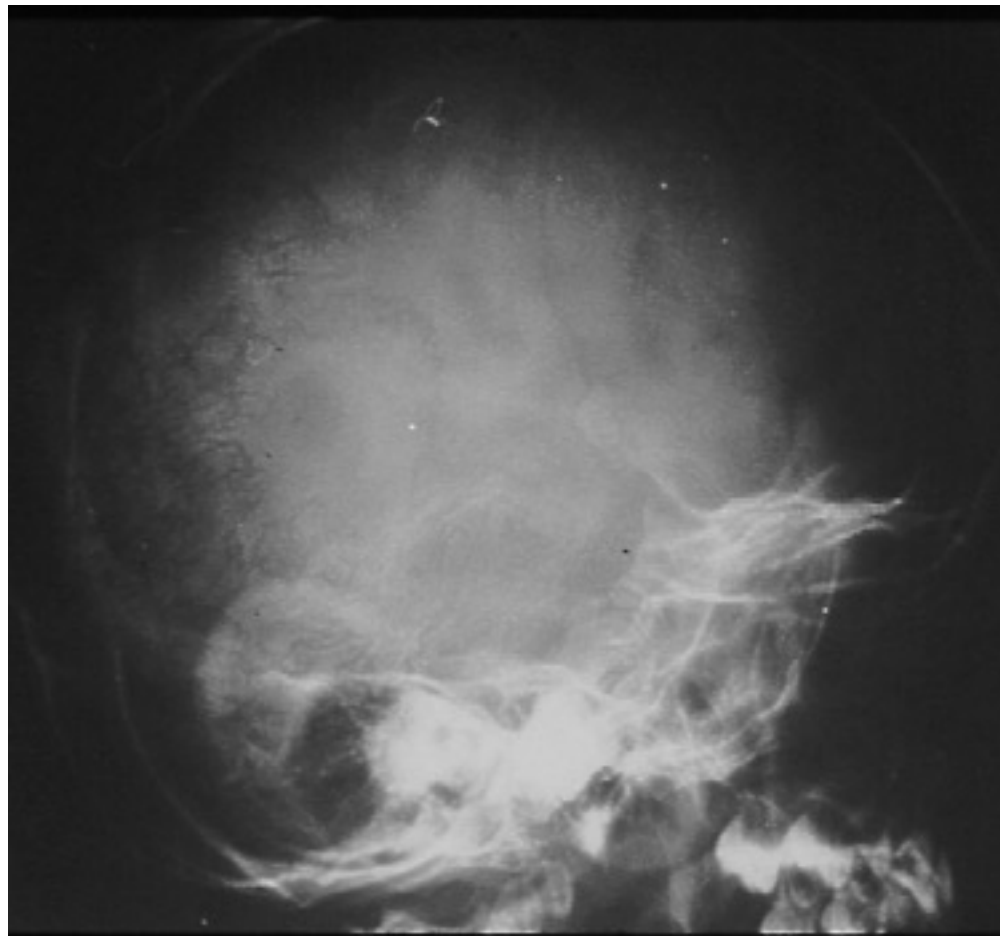
- Diagnosis of osteogenesis imperfecta is based on clinical and radiological findings. BMD as assessed by DXA is usually low. Typical radiological findings include vertebral compression fractures, curvature and fractures of long bones, a generalized decrease in bone density, and thinning of bones.
- In addition to the skeletal findings, blue sclerae, greyish teeth (dentinogenesis imperfecta), and hearing impairment are present in patients with certain types of osteogenesis imperfecta.
- Diagnostic methods include molecular analysis of type I collagen in cultured fibroblasts or genetic studies of relevant genes.

Ossa wormiane

Osteogenesi Imperfetta tipo I

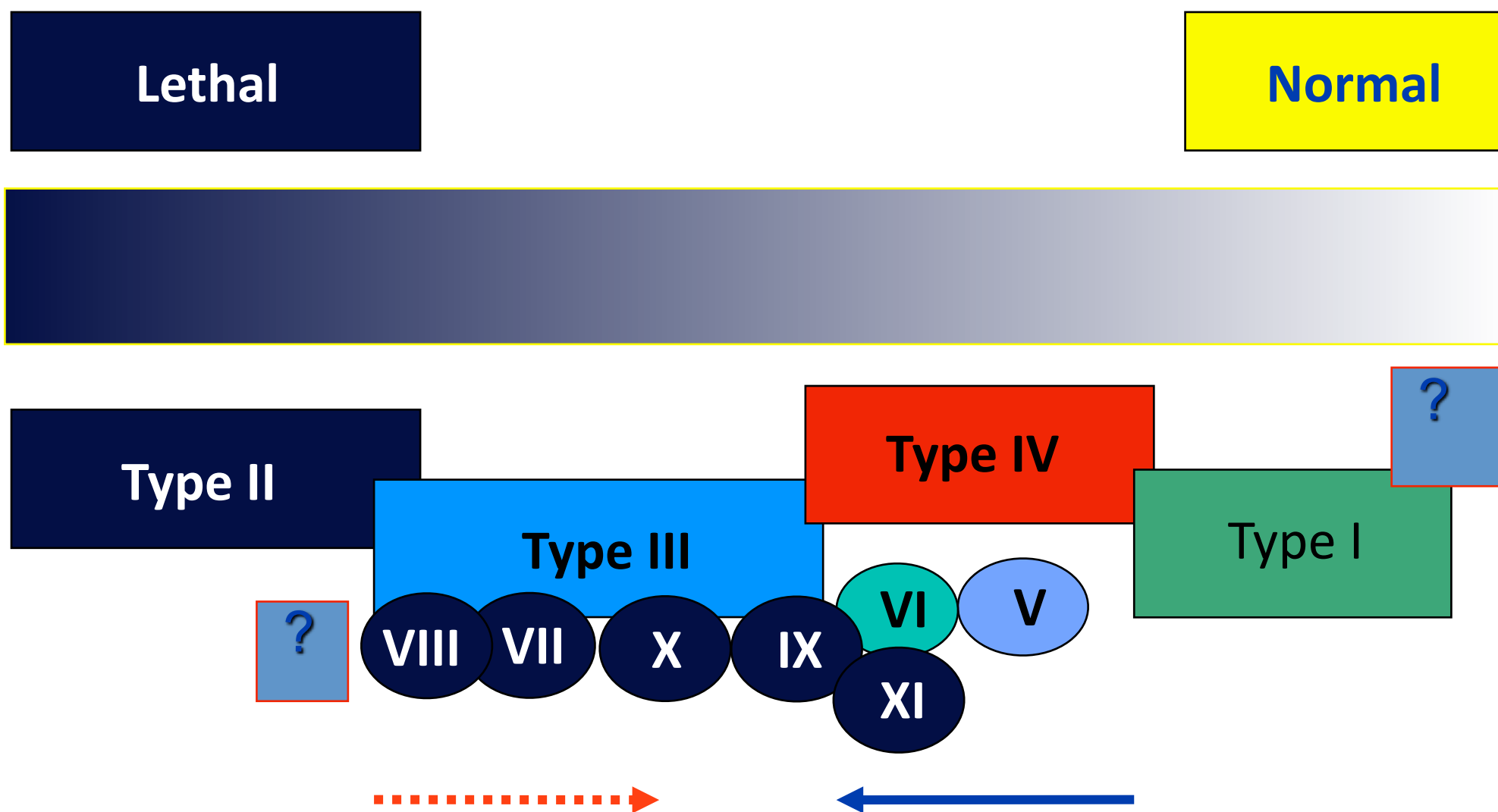
Schiacciamenti vertebrali

a

b

OI tipo I:
cranio con ossa wormiane (a),
frattura diafisaria (b)

Osteogenesis Imperfecta

Most patients with osteogenesis imperfecta have heterozygous mutations in *COL1A1* or *COL1A2*, although causative mutations in several other genes have also been identified; these mutations collectively account for 2–5% of cases of osteogenesis imperfecta.

The spectrum of osteogenesis imperfecta phenotypes ranges from mild (increased fracture risk but no major deformity or height deficit; type I) to very severe (neonatally lethal; type II).

Lethal

Normal

Type II

Type III

Type IV

Type I

?

?

VIII VII X IX XI

VI V

Please cite this article in press as: Pyott et al., *WNT1* Mutations in Families Affected by Moderately Severe and Progressive Recessive Osteogenesis Imperfecta, The American Journal of Human Genetics (2013), http://dx.doi.org/10.1016/j.ajhg.2013.02.009

REPORT

WNT1 Mutations in Families Affected by Moderately Severe and Progressive Recessive Osteogenesis Imperfecta

Shawna M. Pyott,[1,*] Thao T. Tran,[1] Dru F. Leistritz,[1] Melanie G. Pepin,[1] Nancy J. Mendelsohn,[2,3] Renee T. Temme,[2] Bridget A. Fernandez,[4] Solaf M. Elsayed,[5] Ezzat Elsobky,[5] Ishwar Verma,[6] Sreelata Nair,[7] Emily H. Turner,[8] Joshua D. Smith,[8] Gail P. Jarvik,[9] and Peter H. Byers[1,9]

95% of individuals with osteogenesis imperfecta (OI [MIM 166200, 166210, 259420, and 166220]) have dominant mutations in the type I collagen genes, COL1A1 (MIM 120150) and COL1A2 (MIM 120160).
Recessively inherited forms of OI (MIM 613849, 610682, 610915, 259440, 613848, 610968, 613982, 614856, and 615066) account for most of the remainder.
These phenotypes can result from mutations in

(1) genes important for osteoblast differentiation (SP7 [MIM 606633]),
(2) genes encoding proteins that modify collagens or act as chaperones during assembly and secretion of collagens (CRTAP [MIM 605497], LEPRE1 [MIM 610339], PPIB [MIM 123841], SERPINH1 [MIM 600943], FKBP10 [MIM 607063], SERPINF1 [MIM 172860], and BMP1 [MIM 112264]), or
(3) genes that modulate intracellular calcium levels (TMEM38B [MIM 611236]).
Most laboratories that study OI have seen affected families in which the molecular basis remains unsolved.

Osteogenesis Imperfecta: Clinical Diagnosis, Nomenclature and Severity Assessment

F.S. Van Dijk,[1] and D.O. Sillence[2]*

[1]Department of Clinical Genetics, Center for Connective Tissue Disorders, VU University Medical Center, Amsterdam, The Netherlands

[2]Discipline of Genetic Medicine, The Children's Hospital at Westmead Clinical School, Sydney Medical School, University of Sydney, Head Connective Tissue Dysplasia Management Service, The Children's Hospital at Westmead, Sydney, Australia

Manuscript Received: 31 October 2013; Manuscript Accepted: 12 February 2014

Am J Med Genet Part A 164A:1470–1481.

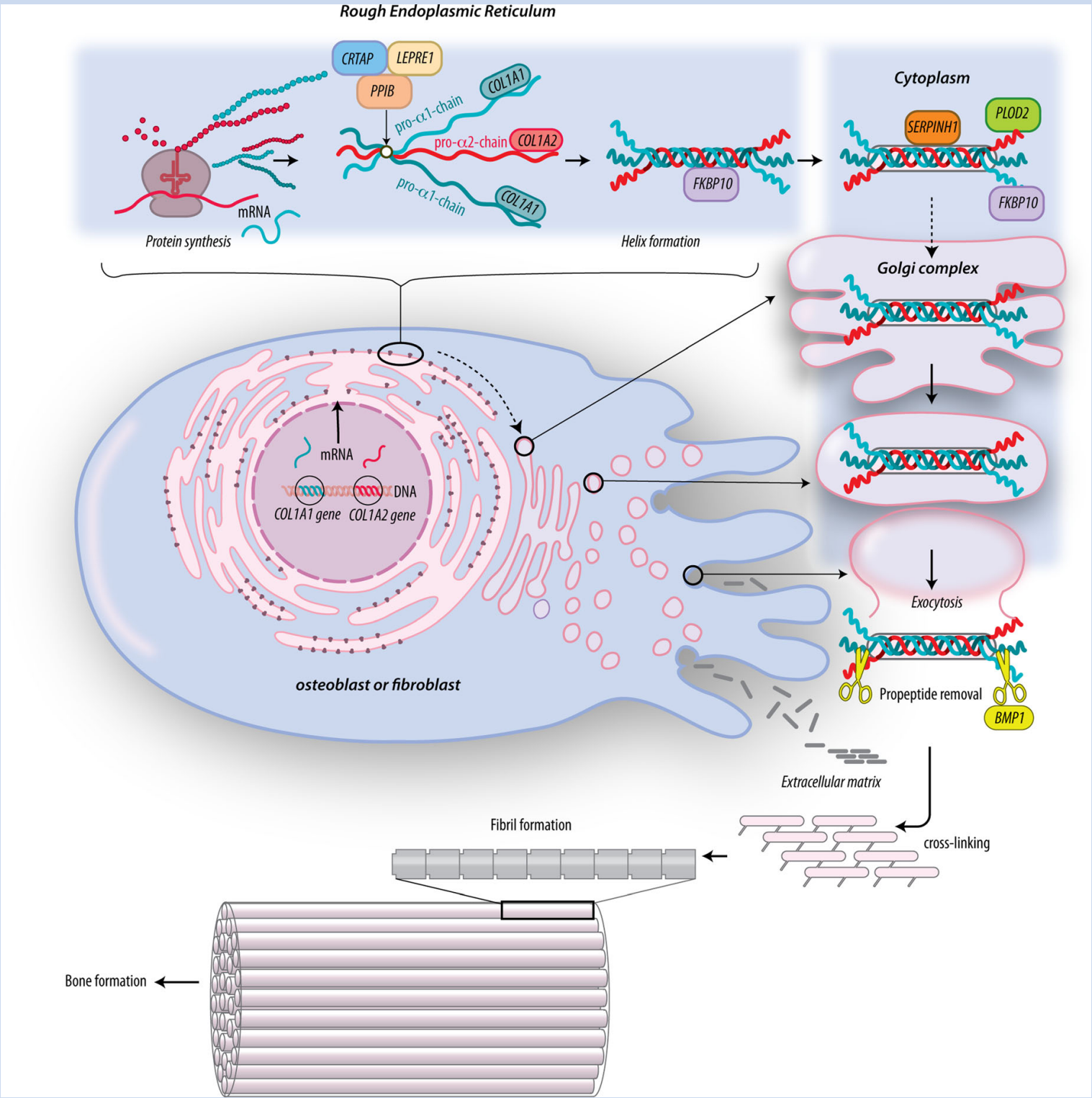



FIG. 1. Overview of collagen type I biosynthesis. Collagen type I consists of two α1-chains and one α2-chain. After translation, pro-α1-chains and pro-α2 chains are processed in the rough Endoplasmic reticulum (rER). These chains have to align in order to start the folding process of (pro)collagen type I into a triple helix. The next step is alignment of the three chains in order to commence folding into a triple helical structure. During this folding process, post-translational modification by specific proteins takes place. The genes encoding proteins involved in post-translational modification and in which mutations have been reported to cause OI, are depicted in this figure. After transport of procollagen type I to the Golgi complex and following exocytosis into the extracellular matrix, cleavage of the C-and N-propeptides results in formation of collagen type I. Subsequently, cross-linking of collagen type I molecules leads to formation of fibrils. Multiple collagen type I fibrils form into collagen fibers, important constituents of bone.

2014 Van Dijk OI

Osteogenesis Imperfecta: Clinical Diagnosis, Nomenclature and Severity Assessment

F.S. Van Dijk,[1] and D.O. Sillence[2]*

[1]Department of Clinical Genetics, Center for Connective Tissue Disorders, VU University Medical Center, Amsterdam, The Netherlands

[2]Discipline of Genetic Medicine, The Children's Hospital at Westmead Clinical School, Sydney Medical School, University of Sydney, Head Connective Tissue Dysplasia Management Service, The Children's Hospital at Westmead, Sydney, Australia

Manuscript Received: 31 October 2013; Manuscript Accepted: 12 February 2014

Am J Med Genet Part A 164A:1470–1481.

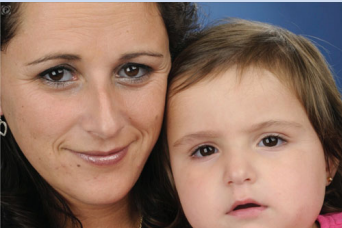
TABLE III. Pre-and Postnatal Severity Grading Scale of Osteogenesis Imperfecta

- Mild OI (Patients with mild OI most often have OI type 1 or 4)
  - Ultrasound findings at 20 weeks of pregnancy
    - No intra-uterine long bone fractures or bowing
  - Postnatal
    - Rarely congenital fractures
    - Normal or near normal growth velocity and height
    - Straight long bones i.e. no intrinsic long bone deformity
    - Fully ambulant other than at times of acute fracture
    - Minimal vertebral crush fractures
    - Lumbar spine bone mineral density *Z*-score usually >-1.5 (-1.5 to $+1.5$)
    - Annualized fracture rate of less than or equal to 1.
    - Absence of chronic bone pain or minimal pain controlled by simple analgesics.
    - Regular school attendance, i.e., does not miss school due to pain, lethargy, or fatigue.

- Moderate OI
  - Ultrasound findings at 20 weeks of pregnancy
    - Rarely fetal long bone fractures or bowing (but may increase in the last trimester)
  - Postnatal (Not modified by bisphosphonate therapy)
    - Occasionally congenital fractures
    - Decreased growth velocity and height
    - Anterior bowing of legs and thighs
    - Bowing of long bones related to immobilization for recurrent fractures
    - Vertebral crush fractures
    - Lumbar spine bone mineral density *Z*-score usually > -2.5 to <-1.5) but a wide range
    - Annualized prepubertal fracture rate greater than 1 (average 3 with a wide range)
    - Absent from school due to pain more than 5 days per year.

- Severe OI
  - Ultrasound findings at 20 weeks of pregnancy
    - Shortening of long bones
    - Fractures and/or bowing of long bones with some under-modeling
    - Slender ribs with absent or discontinuous rib fractures (cases intermediate between severe and extremely severe have few rib fractures but crumpled long bones)
    - Decreased mineralization
  - Postnatal (not modified by bisphosphonate therapy)
    - Marked impairment of linear growth
    - Wheel-chair dependent
    - Progressive deformity of long bones and spine (unrelated to fractures)
    - Multiple vertebral crush fractures
    - Lumbar spine bone mineral density *Z*-score usually <-3.0 (wide range with age comparison as measurement is size/height dependent)
    - Annualized prepubertal fracture rate greater than 3 fractures per annum (age dependent)
    - Chronic bone pain unless treated with bisphosphonates
    - School attendance characterized by absences for fracture care and fatigue or pain

- Extremely Severe OI
  - Ultrasound findings at 20 weeks of pregnancy
    - Shortening of long bones
    - Fractures and/or bowing of long bones with severe under-modeling leading to crumpled (concertina-like) long bones
    - Thick continuously beaded ribs due to multiple sites of fracture or thin ribs (previously described as OI type 2-A and 2-B, respectively)
    - Decreased mineralization
  - Postnatal
    - Thighs held in fixed abduction and external rotation with limitation of movement of most joints
    - Clinical indicators of severe chronic pain (pallor, sweatiness, whimpering or grimacing on passive movement)
    - Decreased ossification of skull, multiple fractures of long bones and ribs. Small thorax.
    - Shortened compacted femurs with a concertina-like appearance
    - All vertebrae hypoplastic/crushed
    - Respiratory distress leading to perinatal death
    - Perinatally lethal course

2014 Van Dijk OI

Primary osteoporosis

- Skeletal homeostasis is controlled by both Wnt–β-catenin and TGFβ–BMP-mediated signalling pathways.
- Mutations in the genes encoding components or targets of these signalling pathways can also result in primary osteoporosis.

Impact of WNT/b-catenin signaling on bone cells.

WNT signaling translates mechanosignals in osteocytes

WNT signaling in bone homeostasis and disease: from human mutations to treatment

Roland Baron[1,2] & Michaela Kneissel[3]

NATURE MEDICINE VOLUME 19 | NUMBER 2 | FEBRUARY 2013

2013 Baron WNT signaling in bone homeostasis

Figure 4

JMG Online First, published on February 23, 2013 as 10.1136/jmedgenet-2013-101567
Genotype-phenotype correlations

SHORT REPORT

Mutations in WNT1 are a cause of osteogenesis imperfecta

Somayyeh Fahiminiya,[1] Jacek Majewski,[1] John Mort,[2] Pierre Moffatt,[2] Francis H Glorieux,[2] Frank Rauch[2]

Please cite this article in press as: Pyott et al., *WNT1* Mutations in Families Affected by Moderately Severe and Progressive Recessive Osteogenesis Imperfecta, The American Journal of Human Genetics (2013), http://dx.doi.org/10.1016/j.ajhg.2013.02.009

REPORT

WNT1 Mutations in Families Affected by Moderately Severe and Progressive Recessive Osteogenesis Imperfecta

Shawna M. Pyott,[1,*] Thao T. Tran,[1] Dru F. Leistritz,[1] Melanie G. Pepin,[1] Nancy J. Mendelsohn,[2,3] Renee T. Temme,[2] Bridget A. Fernandez,[4] Solaf M. Elsayed,[5] Ezzat Elsobky,[5] Ishwar Verma,[6] Sreelata Nair,[7] Emily H. Turner,[8] Joshua D. Smith,[8] Gail P. Jarvik,[9] and Peter H. Byers[1,9]

The NEW ENGLAND JOURNAL *of* MEDICINE

BRIEF REPORT

WNT1 Mutations in Early-Onset Osteoporosis and Osteogenesis Imperfecta

Christine M. Laine, M.D., Ph.D., Kyu Sang Joeng, Ph.D., Philippe M. Campeau, M.D., Riku Kiviranta, M.D., Ph.D., Kati Tarkkonen, Ph.D., Monica Grover, M.D., James T. Lu, B.S., Minna Pekkinen, Ph.D., Maija Wessman, Ph.D., Terhi J. Heino, Ph.D., Vappu Nieminen-Pihala, M.Sc., Mira Aronen, Tero Laine, M.D., Ph.D., Heikki Kröger, M.D., Ph.D., William G. Cole, M.D., Ph.D., Anna-Elina Lehesjoki, M.D., Ph.D., Lisette Nevarez, B.S., Deborah Krakow, M.D., Cynthia J.R. Curry, M.D., Daniel H. Cohn, Ph.D., Richard A. Gibbs, Ph.D., Brendan H. Lee, M.D., Ph.D., and Outi Mäkitie, M.D., Ph.D.

N Engl J Med 2013;368:1809-16.

Please cite this article in press as: Keupp et al., Mutations in *WNT1* Cause Different Forms of Bone Fragility, The American Journal of Human Genetics (2013), http://dx.doi.org/10.1016/j.ajhg.2013.02.010

ARTICLE

Mutations in *WNT1* Cause Different Forms of Bone Fragility

Katharina Keupp,[1,2,3] Filippo Beleggia,[1,2,3] Hülya Kayserili,[4] Aileen M. Barnes,[5] Magdalena Steiner,[6] Oliver Semler,[7] Björn Fischer,[6] Gökhan Yigit,[1,2,3] Claudia Y. Janda,[8] Jutta Becker,[1] Stefan Breer,[9] Umut Altunoglu,[4] Johannes Grünhagen,[6] Peter Krawitz,[6] Jochen Hecht,[10] Thorsten Schinke,[9] Elena Makareeva,[11] Ekkehart Lausch,[12] Tufan Cankaya,[13] José A. Caparrós-Martín,[14,15] Pablo Lapunzina,[15,16] Samia Temtamy,[17] Mona Aglan,[17] Bernhard Zabel,[12] Peer Eysel,[18] Friederike Koerber,[19] Sergey Leikin,[11] K. Christopher Garcia,[8] Christian Netzer,[1] Eckhard Schönau,[7] Victor L. Ruiz-Perez,[14,15] Stefan Mundlos,[6,20] Michael Amling,[9] Uwe Kornak,[6,20,*] Joan Marini,[5] and Bernd Wollnik[1,2,3,*]

Causes, mechanisms and management of paediatric osteoporosis
Outi Mäkitie
NATURE REVIEWS | RHEUMATOLOGY

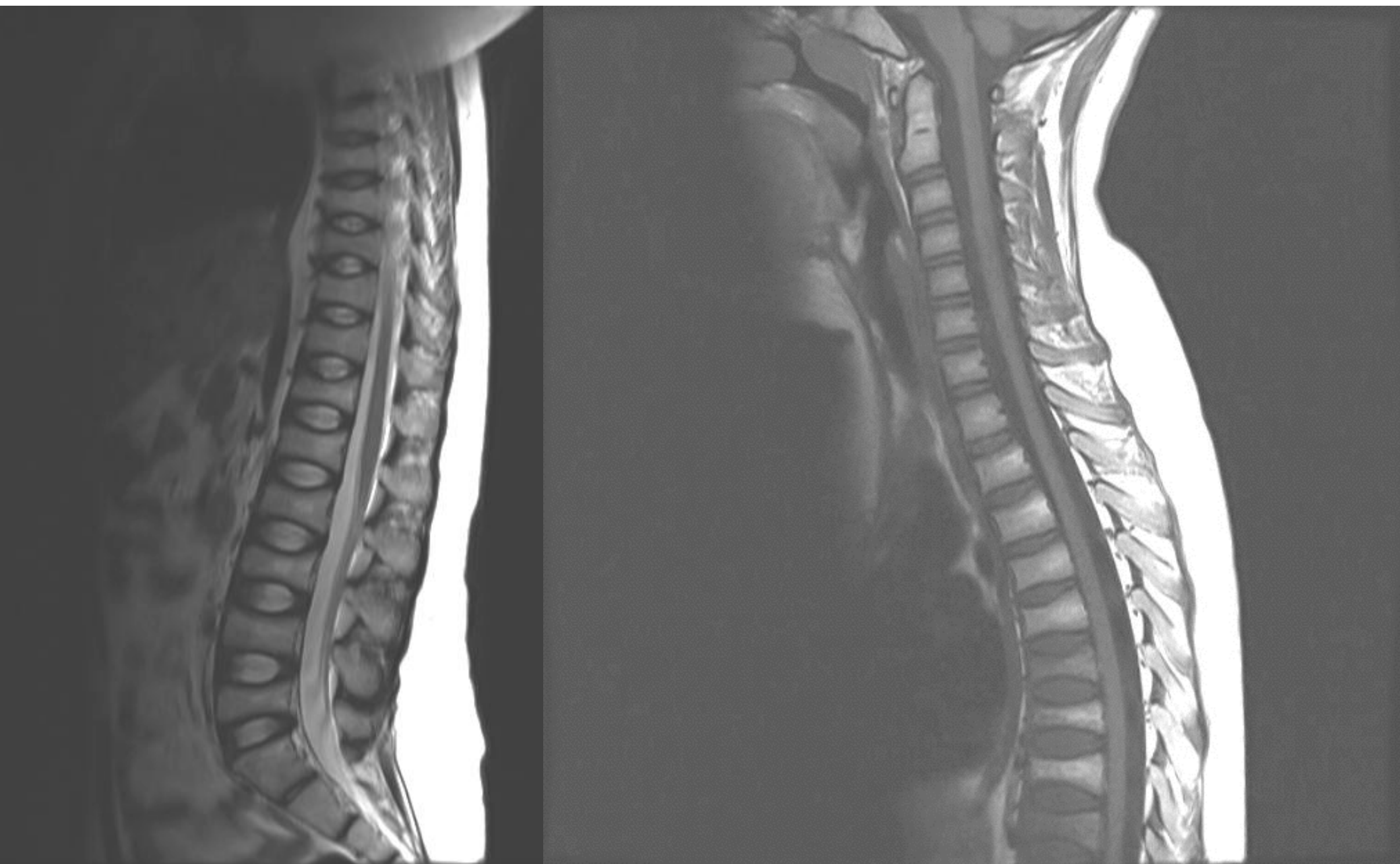
Table 1 Conditions associated with childhood-onset primary osteoporosis

WNT System

Condition	Underlying genes	Disease mechanism	Mode of inheritance	Phenotype MIM number
Osteogenesis imperfecta (types I, II, III and IV)	*COL1A1, COL1A2*	Defect in type I collagen	AD	166200, 166210, 259420, 166220
Osteogenesis imperfecta (type V)	*IFITM5*	Dysregulation of bone formation	AD	610967
Osteogenesis imperfecta (type VI)	*SERPINF1*	Mineralization defect	AR	613982
Osteogenesis imperfecta (type VII)	*CRTAP*	Collagen prolyl 3-hydroxylation defect	AR	610682
Osteogenesis imperfecta (type VIII)	*LEPRE1*	Collagen prolyl 3-hydroxylation defect	AR	610915
Osteogenesis imperfecta (type IX)	*PPIB*	Collagen prolyl 3-hydroxylation defect	AR	259440
Osteogenesis imperfecta (type X)	*SERPINH1*	Chaperone defects	AR	613848
Osteogenesis imperfecta (type XI)	*FKBP10*	Chaperone defects	AR	610968
Osteogenesis imperfecta (type XII)	*SP7*	Impaired osteoblast differentiation	AR	613849
Osteogenesis imperfecta (type XIII)	*BMP1*	Defective collagen processing	AR	614856
Bruck syndrome	*PLOD2*	Impaired collagen cross-link formation	AR	609220
Osteoporosis–pseudoglioma syndrome	*LRP5*	Impaired Wnt signalling and osteoblast function	AR	259770
Ehlers–Danlos syndrome	*COL5A1, COL5A2, TNXB, COL3A1*	Defects in connective tissue	AD	130020 130050
Marfan syndrome	*FBN1, TGFBR2*	Defects in connective tissue	AD	154700
Cleidocranial dysplasia	*RUNX2*	Impaired bone formation	AD	119600
Calvarial doughnut lesions	Unknown	Unknown	AD	126550
Spondylo-ocular syndrome	Unknown	Unknown	AR	605822
Hajdu–Cheney syndrome	*NOTCH2*	Abnormal bone remodelling	AD	102500
Primary osteoporosis	*LRP5*	Impaired Wnt signalling and osteoblast function	AD	166710
Primary osteoporosis	*LRP6*	Impaired Wnt signalling and osteoblast function	AD	610947
Idiopathic juvenile osteoporosis	Unknown	Unknown	Unknown	259750

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MIM, Mendelian Inheritance in Man.

Idiopathic juvenile osteoporosis

- Idiopathic juvenile osteoporosis, in which the cause of osteoporosis is unknown, is inadequately characterized and poorly defined.
- Onset of the condition usually occurs before puberty and patients typically present with bone pain and walking difficulties; compression fractures and metaphyseal fractures are often present at diagnosis.
- Histomorphometric analyses showed decreased trabecular bone volume with decreased number and thickness of trabeculae in these individuals, suggesting a modelling defect that primarily affects bone surfaces in contact with the bone marrow cavity. In contrast to other forms of primary osteoporosis, idiopathic juvenile osteoporosis can resolve spontaneously by early adulthood.

Osteoporosi Idiopatica Giovanile

2.3 - Secondary Osteoporosis

“new” secondary bone pathologies in children and adolescents

- Neoplastic diseases
- Transplants (liver, BMT, stem cells)
- Cerebral Palsy, DMD
- Antihepileptic therapies
- Anorexia Nervosa
- Chronic disease
  - Bowel Inflammatory disease
  - Cistic fibrosis
  - IJA
- Low birth weight
- …

Causes, mechanisms and management of paediatric osteoporosis
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NATURE REVIEWS | RHEUMATOLOGY

Figure 2 | Factors linked to osteoporosis in children with an underlying chronic illness. Features of the underlying disease itself, including endocrine dysfunction, malnutrition, or impaired liver or kidney function, can predispose children to osteoporosis. Factors resulting from the disease, including changes in lifestyle, musculoskeletal disorders, and pharmacological treatments can also lead to osteoporosis. Abbreviations: JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Limited exposure to sunlight
Inadequate vitamin D intake
Inadequate calcium intake
Malnutrition
Malabsorption
Eating disorders

Growth hormone deficiency
Hypogonadism
Turner syndrome
Delayed puberty
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism

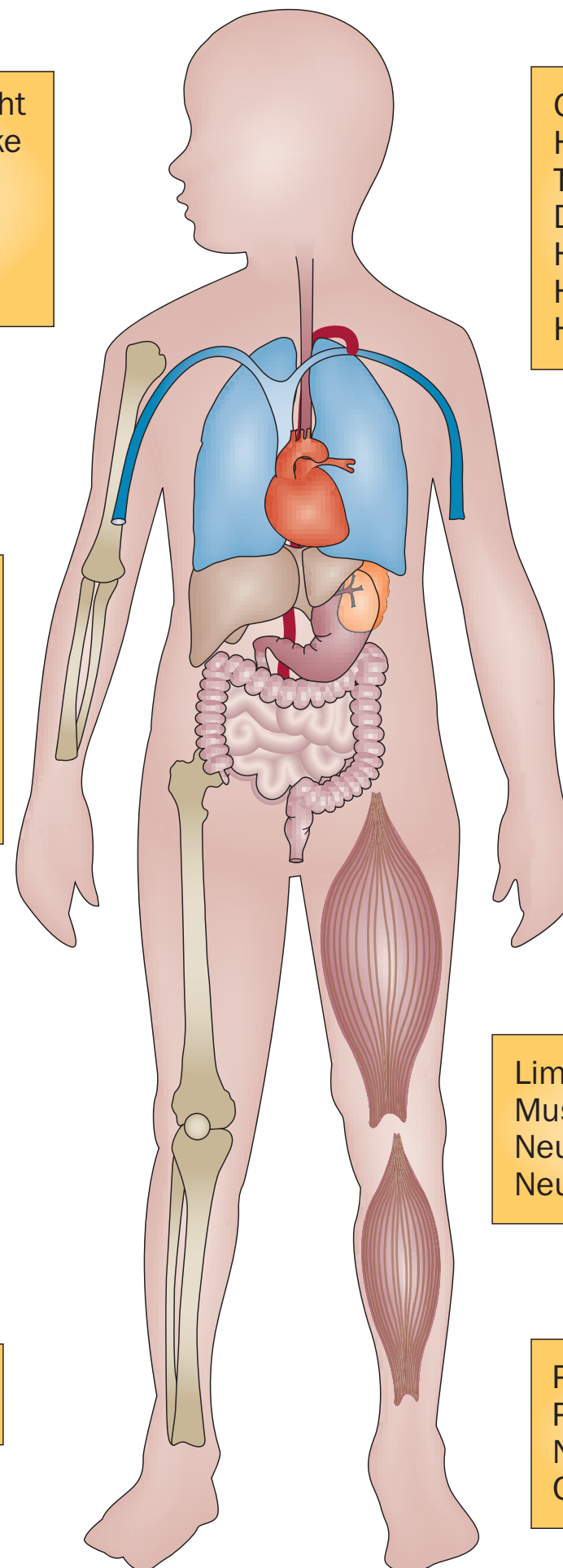
Glucocorticoids
Antiepileptic drugs
Calcineurin inhibitors
Anticoagulants
Methotrexate
Gonadotropin-releasing hormone agonists

Chronic inflammation
Kidney insufficiency
Liver insufficiency
Hypoxia

Leukaemia
Thalassaemia
JIA
SLE

Limited weight-bearing activity
Muscle weakness
Neurological impairment
Neuromuscular disorders

Organ transplantation
Stem-cell transplantation

Prenatal factors
Preterm birth
Neonatal infection
Compromised lung function

Secondary osteoporosis

Contributing factors

- *(Fetal) Development*
- *Immobility*
- *Endocrine dysfunction*
- *Nutritional factors*
- *Underlying illness*
- *Treatments*

Underlying illness and Treatments

- In children with an underlying chronic illness, optimal control of the primary disease is the cornerstone of both prevention and treatment of osteoporosis.
- The potential adverse skeletal effects of the available treatments should be taken into consideration and excessive use of systemic glucocorticoids in particular should be avoided.

Decreased Bone Mineral Density in Adults Born with Very Low Birth Weight: A Cohort Study

Petteri Hovi[1,2*], Sture Andersson[1], Anna-Liisa Järvenpää[1], Johan G. Eriksson[2,3,4], Sonja Strang-Karlsson[1,2], Eero Kajantie[1,2], Outi Mäkitie[1]

1 Hospital for Children and Adolescents, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland, 2 Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland, 3 Department of General Practice and Primary Health Care, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland, 4 Vasa Central Hospital, Vasa, Finland

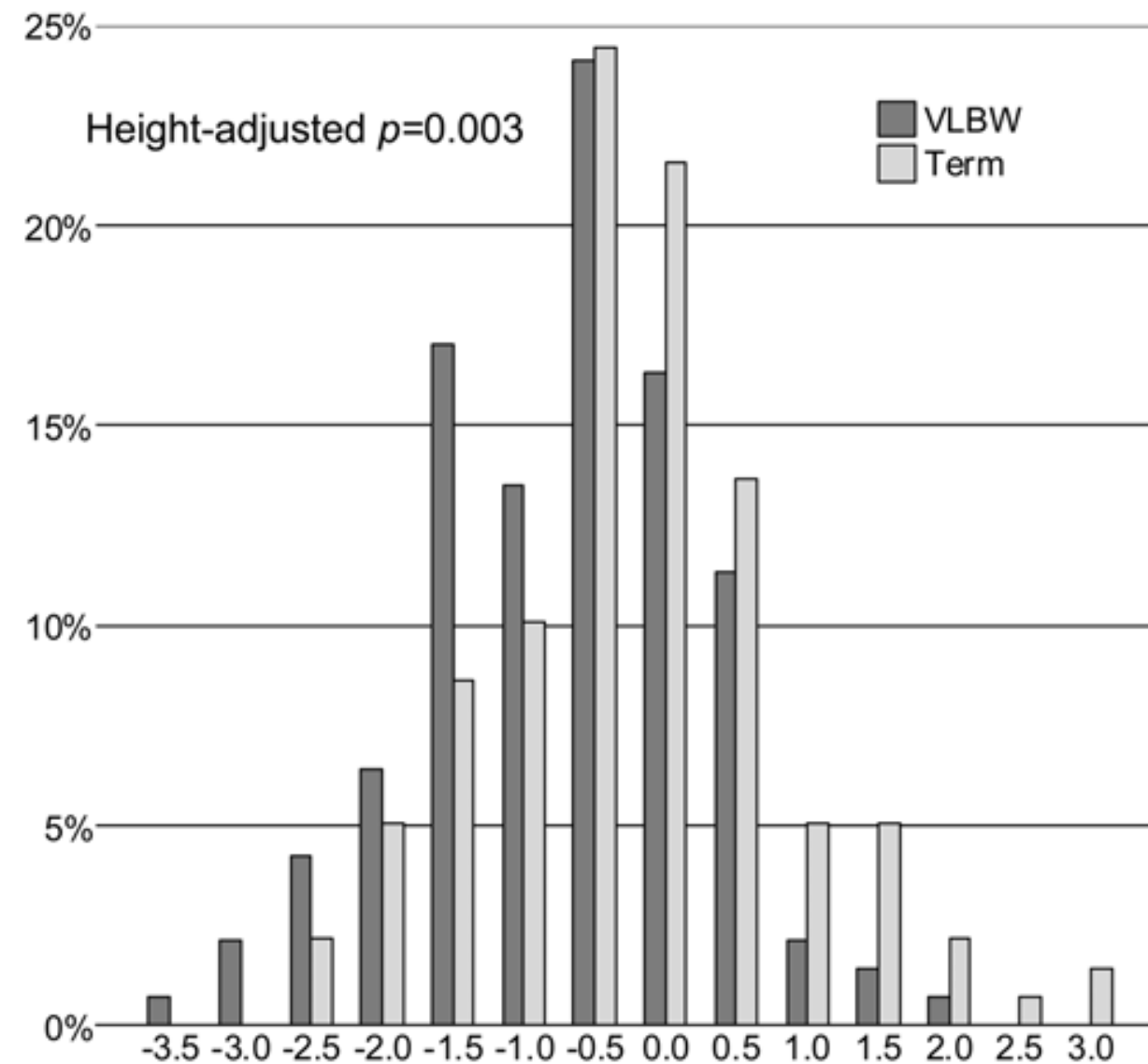



Figure 2. Lumbar spine BMD distributions in VLBW and term-born young adults. Mean lumbar spine BMD Z score, as provided by the absorptiometry equipment, was lower in the 141 young adults with VLBW ($<$1,500 g), dark bars, than in the 139 term-born comparison participants ($p<0.001$). Each category includes and is denoted by its' highest value.
doi:10.1371/journal.pmed.1000135.g002

2009 Hovi LBW Bone

CLINICAL CASE REPORT

Bone Health in Adolescent Females with Anorexia Nervosa: What is a Clinician to Do?

Debra K. Katzman, MD, FRCPC[1]*
Madhusmita Misra, MD, MPH[2]

ABSTRACT
The objective of this case report is to present a pharmacologic strategy for treatment of adolescents with anorexia nervosa (AN) and low bone mineral density (BMD). We present a 17.5-year-old girl with a 3-year history of AN and longstanding inability to optimize nutrition and gain weight, and a decrease over time in her already low BMD. A year after treatment with the 17-β estradiol patch (100 mcg twice weekly) with cyclic oral progesterone (2.5 mg medroxyprogesterone acetate daily for days 1–10 of every month), her spine and hip BMD Z-scores improved, and a further decrease was prevented. This novel treatment is a consideration for girls with AN at greatest risk for low BMD. Adolescents with AN are at risk for low BMD, and the most effective treatment is weight and menses restoration, which can be difficult to attain and to sustain. Recent studies have shown promising results with pharmacological therapy for low BMD in AN. This article discusses current concepts related to bone loss in AN, and new pharmacologic considerations for adolescents at greatest risk for low BMD.

Keywords: anorexia nervosa; adolescence; bone mineral density; estrogen; insulin-like growth factor-1

(Int J Eat Disord 2013; 46:456–460)

2013 Katzman AN

Haematological malignancies

- Children with haematological malignancies or those who have undergone stem cell transplantation often have bone loss caused by either glucocorticoid use or disease-related factors such as leukaemic infiltration.
- Children with acute lymphoblastic leukaemia have low bone mass and an increased fracture rate at diagnosis, as well as during and after therapy.

LAL

- During a 12-month prospective follow-up study of children with acute lymphoblastic leukaemia, 16% of the 155 children developed incident vertebral fractures; a low BMD Z-score or vertebral fractures at baseline substantially increased the probability of incident vertebral fractures during the following year.

18/05/00

22/06/00

04/10/00

LAL

Iranian Red Crescent Medical Journal

CASE REPORT

Initial Presentation of Acute Lymphoblastic Leukemia with Osteoporosis and Multiple Spontaneous Bone Fractures

N Cohan[1], S Sarikhani[2], S Moslemi[2], M Karimi[1]*

[1]Hematology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
[2]College of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Iran Red Crescent Med J 2011; 13(1):52-54

Fig. 1: Bone fractures in patient with ALL.

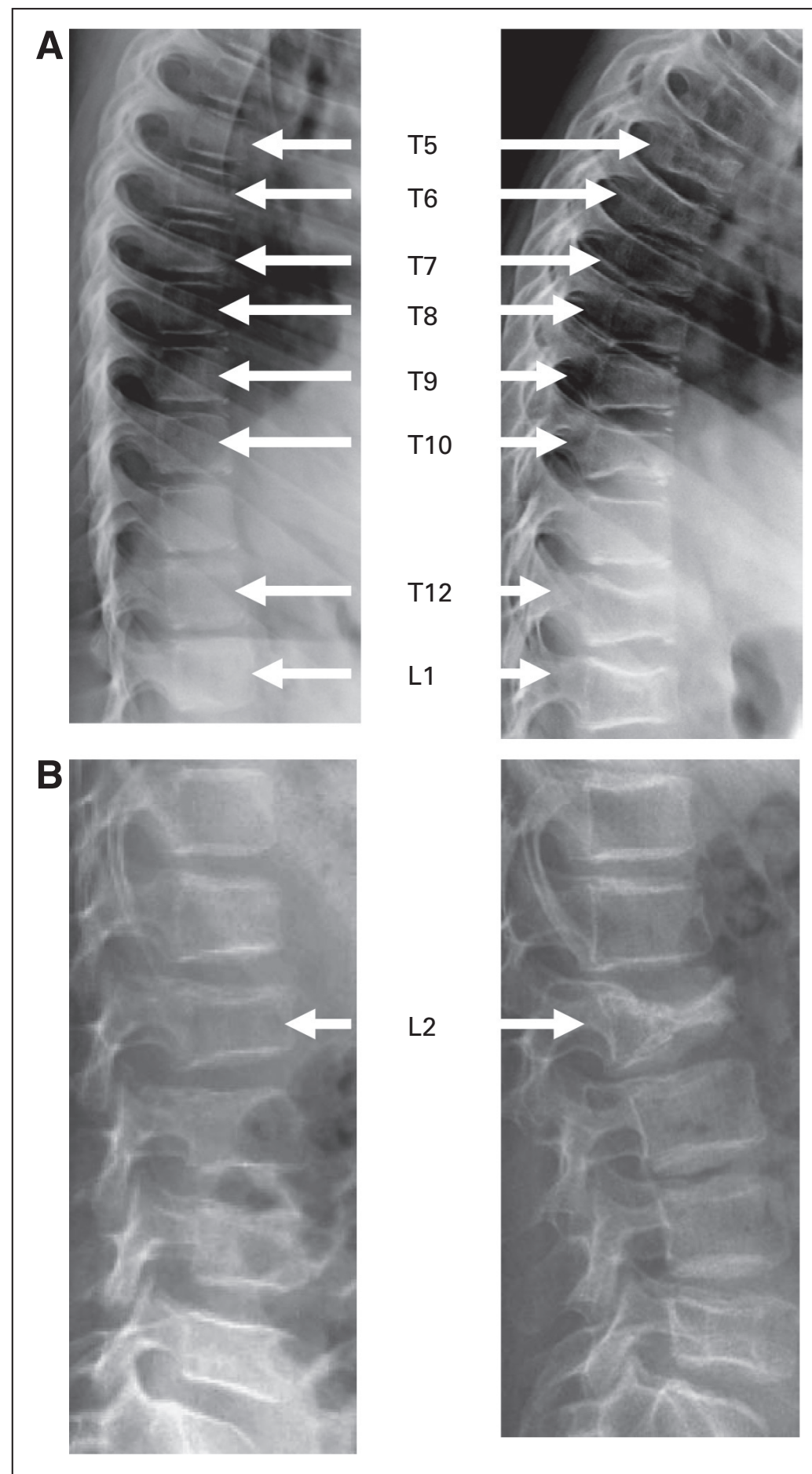
2011 Cohan LAL Bone

VOLUME 30 · NUMBER 22 · AUGUST 1 2012

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

High Incidence of Vertebral Fractures in Children With Acute Lymphoblastic Leukemia 12 Months After the Initiation of Therapy

Nathalie Alos, Ronald M. Grant, Timothy Ramsay, Jacqueline Halton, Elizabeth A. Cummings, Paivi M. Miettunen, Sharon Abish, Stephanie Atkinson, Ronald Barr, David A. Cabral, Elizabeth Cairney, Robert Couch, David B. Dix, Conrad V. Fernandez, John Hay, Sara Israels, Caroline Laverdière, Brian Lentle, Victor Lewis, MaryAnn Matzinger, Celia Rodd, Nazih Shenouda, Robert Stein, David Stephure, Shayne Taback, Beverly Wilson, Kathryn Williams, Frank Rauch, Kerry Siminoski, and Leanne M. Ward

Fig 2. Representative incident vertebral fractures at 12 months after initiation of therapy for pediatric acute lymphoblastic leukemia. (A) Left panel shows a 9-year-old girl at baseline with a normal spine radiograph. At 12 months (right panel), she has multiple incident vertebral fractures (a severe fracture at T5; moderate fractures at T10, T12, and L1; and mild fractures at T6, T7, T8, and T9). (B) Left panel shows a 9-year-old boy at baseline with a moderate L2 fracture. At 12 months (right panel), the L2 deformity has progressed to a severe fracture.

Mini Review

HORMONE
RESEARCH

Horm Res 2005;64:209–221
DOI: 10.1159/000088976

Published online: October 14, 2005

Osteoporosis due to Glucocorticoid Use in Children with Chronic Illness

Leanne M. Ward

Department of Pediatrics, University of Ottawa and Division of Endocrinology, Children's Hospital of Eastern Ontario, Ottawa, Canada

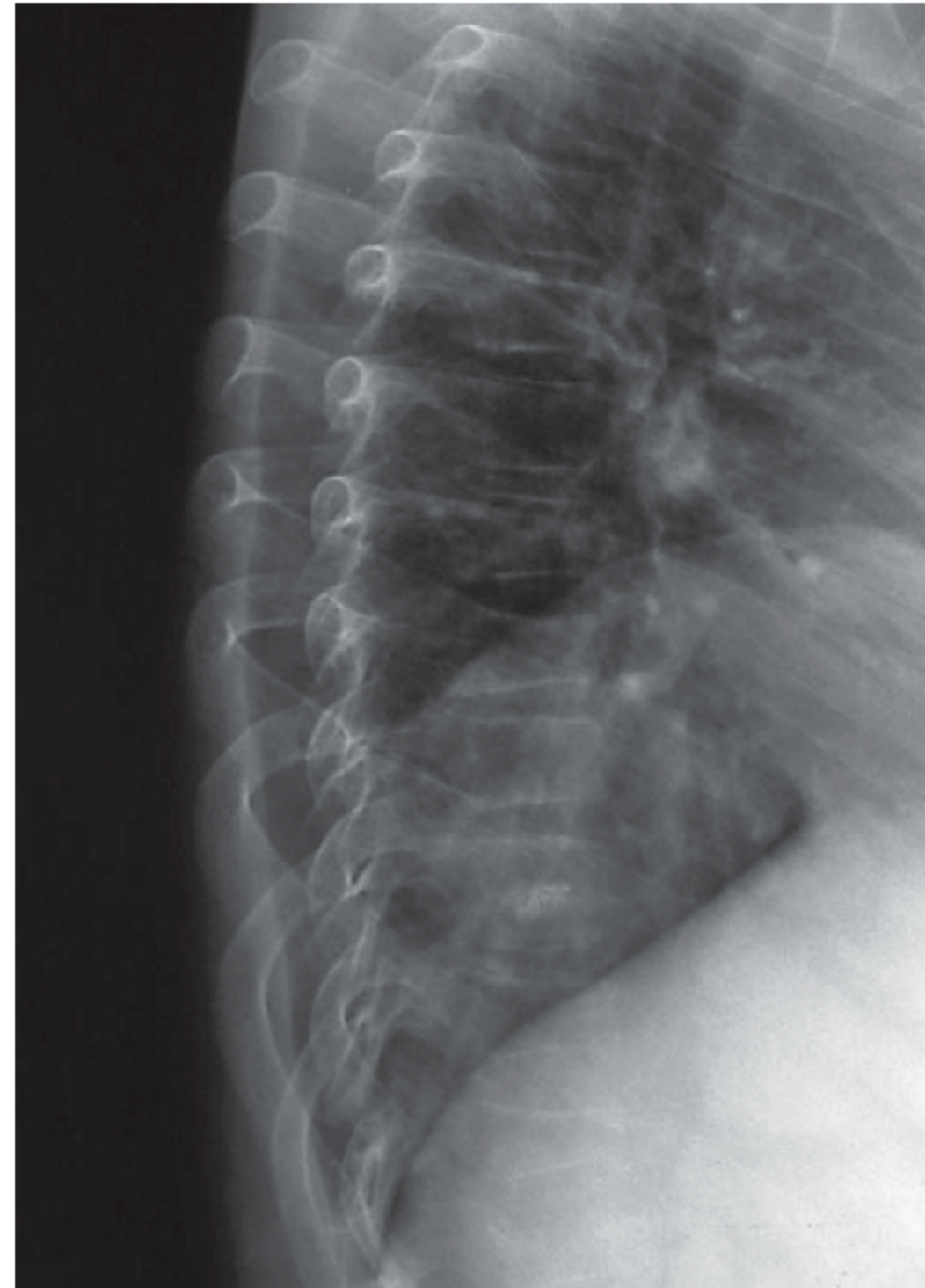



Fig. 1. Vertebral compression following 5 years' deflazacort use, given to retard deterioration in muscle strength in a 13-year-old patient with Duchenne's muscular dystrophy.

Mini Review

HORMONE
RESEARCH

Horm Res 2005;64:209–221
DOI: 10.1159/000088976

Published online: October 14, 2005

Osteoporosis due to Glucocorticoid Use in Children with Chronic Illness

Leanne M. Ward

Department of Pediatrics, University of Ottawa and Division of Endocrinology, Children's Hospital of Eastern Ontario, Ottawa, Canada

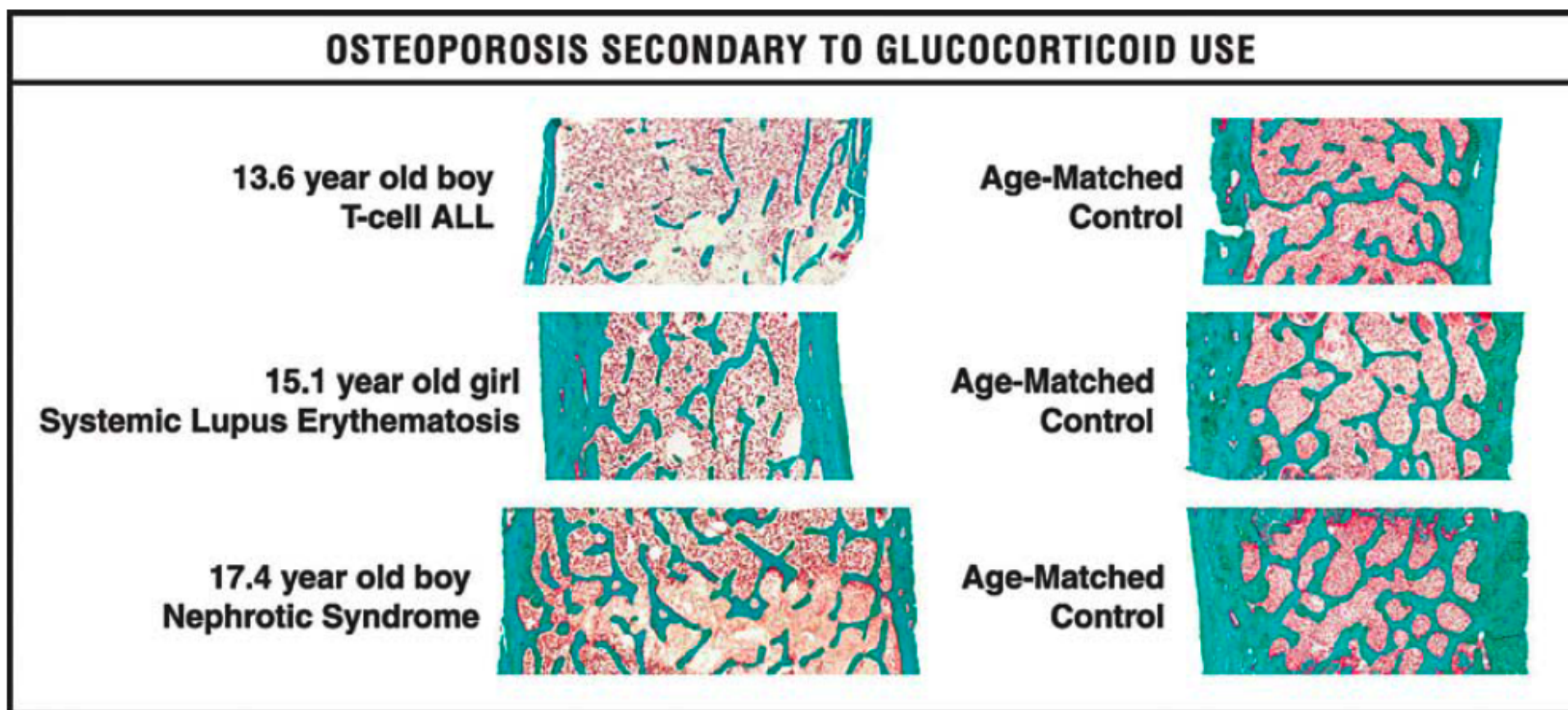



Fig. 2. Qualitative ilial histomorphometry in children with glucocorticoid-induced osteoporosis, with results compared to healthy controls. T-cell ALL = T-cell acute lymphoblastic leukemia.

Causes, mechanisms and management of paediatric osteoporosis

Outi Mäkitie

NATURE REVIEWS | RHEUMATOLOGY

Normal bone remodelling

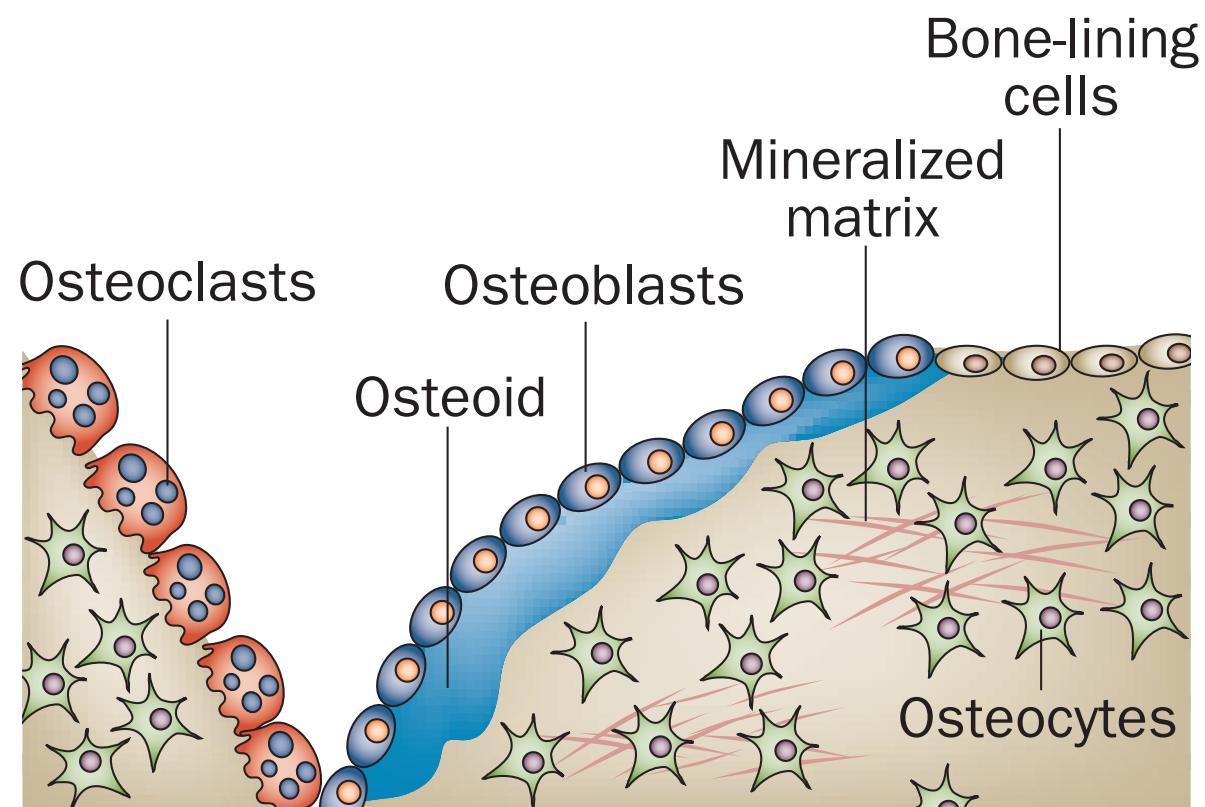
Bone-lining cells

Mineralized matrix

Osteoclasts

Osteoblasts

Osteoid

Osteocytes

Abnormal bone remodelling

- Decreased number of osteoblasts
- Increased apoptosis
- Incomplete bone repair

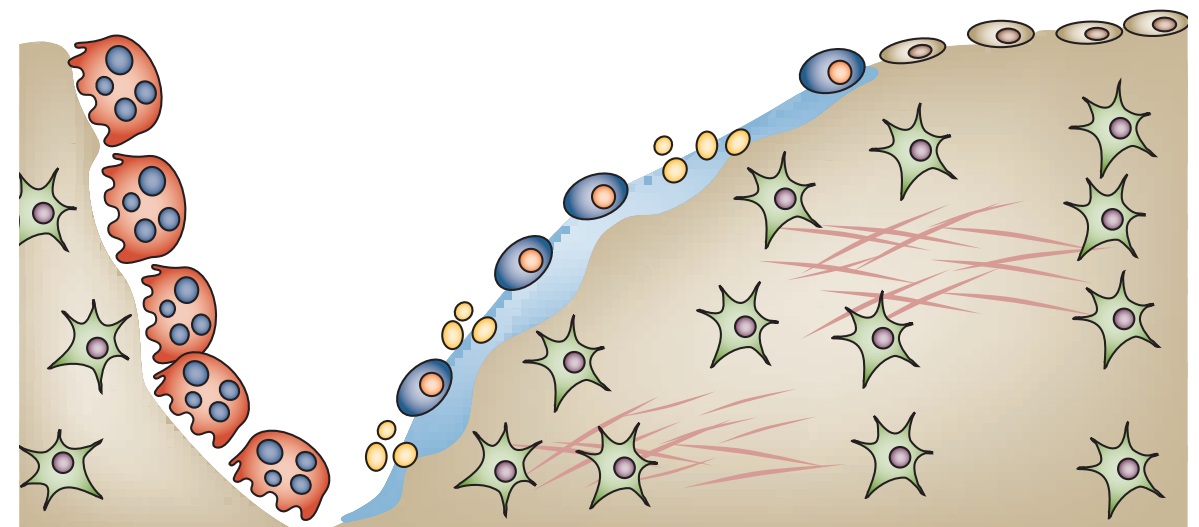



Figure 3 | Glucocorticoids induce abnormal bone remodelling. Normal bone remodelling is the coordinated process of bone resorption followed by new bone formation (left panel). Osteoclasts, the multinucleated cells responsible for bone resorption, release hydrogen ions and enzymes to break down bone's organic matrix. The bone-forming cells, osteoblasts, produce the collagenous matrix, or the osteoid, which is subsequently mineralized. Osteoblasts entrapped in the mineralized matrix develop into osteocytes, mature bone cells that participate in matrix maintenance and mineral homeostasis, and communicate with osteoblasts via cytoplasmic processes. Glucocorticoids initially increase bone resorption because of increased osteoclast survival and indirect glucocorticoid effects including decreased intestinal calcium absorption, increased calciuria and decreased synthesis of sex steroids and insulin-like growth factor I. Long-term glucocorticoid exposure leads to decreased bone formation (right panel) by inducing apoptosis of mature osteoblasts and osteocytes. Consequently, there is a reduction in the number of bone-forming cells, and the amount of bone replaced in each remodelling cycle becomes insufficient to counterbalance increased bone resorption.

Review
CellPress

Feature Review

Glucocorticoids and bone: local effects and systemic implications

Holger Henneicke[1*], Sylvia J. Gasparini[1*], Tara C. Brennan-Speranza[1], Hong Zhou[1], and Markus J. Seibel[1,2]

[1] Bone Research Program, The Australian and New Zealand Army Corps (ANZAC) Research Institute, The University of Sydney, Sydney, Australia
[2] Department of Endocrinology and Metabolism, Concord Hospital, The University of Sydney, Sydney, Australia

Trends in Endocrinology and Metabolism, April 2014, Vol. 25, No. 4

GC excess

Osteoblasts

↓ Differentiation
Proliferation
Function

↑ Cell cycle arrest
Apoptosis

Wnt ↓

OPG ↓
RANKL ↑

MSC

↓ β-Catenin

Osteocytes

↑ Apoptosis

Osteoclasts

↑ Differentiation

Apoptosis
↓ Cytoskeletal reorganization
Proliferation of precursors

Adipocytes

↑ Differentiation

2014 Henneicke GC Osteoporosis

Review

CellPress

Feature Review

Glucocorticoids and bone: local effects and systemic implications

Holger Henneicke[1*], Sylvia J. Gasparini[1*], Tara C. Brennan-Speranza[1], Hong Zhou[1], and Markus J. Seibel[1,2]

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Trends in Endocrinology and Metabolism, April 2014, Vol. 25, No. 4

2014 Henneicke GC Osteoporosis

0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(3):1888–1896

doi: 10.1210/jc.2004-1629

CONSENSUS STATEMENT: Guide to Bone Health and Disease in Cystic Fibrosis

Robert M. Aris,* Peter A. Merkel,* Laura K. Bachrach, Drucy S. Borowitz, Micheal P. Boyle, Sarah L. Elkin, Theresa A. Guise, Dana S. Hardin, Charles S. Haworth, Michael F. Holick, Patricia M. Joseph, Kimberly O'Brien, Elizabeth Tullis, Nelson B. Watts, and Terry B. White

Pulmonary Medicine and Cystic Fibrosis/Pulmonary Research and Treatment Center (R.M.A.), University of North Carolina, Chapel Hill, North Carolina 27599; Divisions of Rheumatology and Endocrinology (P.A.M., M.F.H.), Boston University, Boston, Massachusetts 02118; Pediatric Endocrinology (L.K.B.), Stanford University, Palo Alto, California 94304; Pediatric Gastroenterology (D.S.B.), State University of New York, Buffalo, New York 14214; Division of Pulmonary and Critical Care Medicine (M.P.B.) and Center for Human Nutrition (K.O.), Johns Hopkins University, Baltimore, Maryland 21205; Endocrinology Division (S.L.E.), Royal Brompton CF Unit, London SW3 6NP, United Kingdom; Division of Endocrinology (T.A.G.), University of Virginia, Charlottesville, Virginia 22908; Pediatric Endocrinology Division (D.S.H.), University of Texas, Dallas, Texas 75390; Manchester Adult CF Unit (C.S.H.), Manchester M13 9WL, United Kingdom; Divisions of Endocrinology and Pulmonary Medicine (P.M.J., N.B.W.), University of Cincinnati, Cincinnati, Ohio 45267; Division of Respirology (E.T.), University of Toronto, Toronto, Canada M5B 1W8; and Cystic Fibrosis Foundation (T.B.W.), Bethesda, Maryland 20814
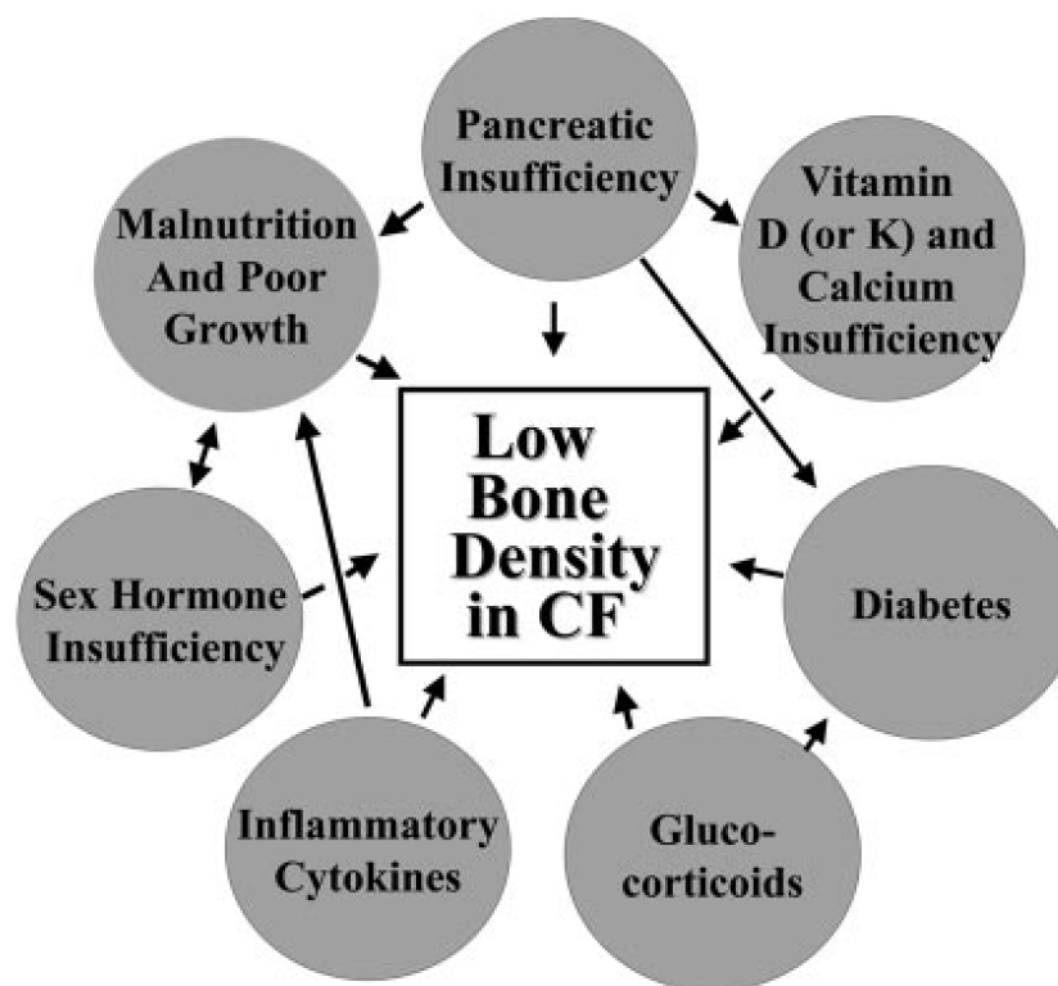
FIG. 1. Pathogenesis of bone disease in CF.

Bone Health in Children With Cerebral Palsy and Epilepsy

Elizabeth Aronson, MNSc, APN, PNP-BC,
& Sharon B. Stevenson, DNP, APN, PNP-BC

J Pediatr Health Care. (2012) *26*, 193-199.

Bone Health in Children With Cerebral Palsy and Epilepsy

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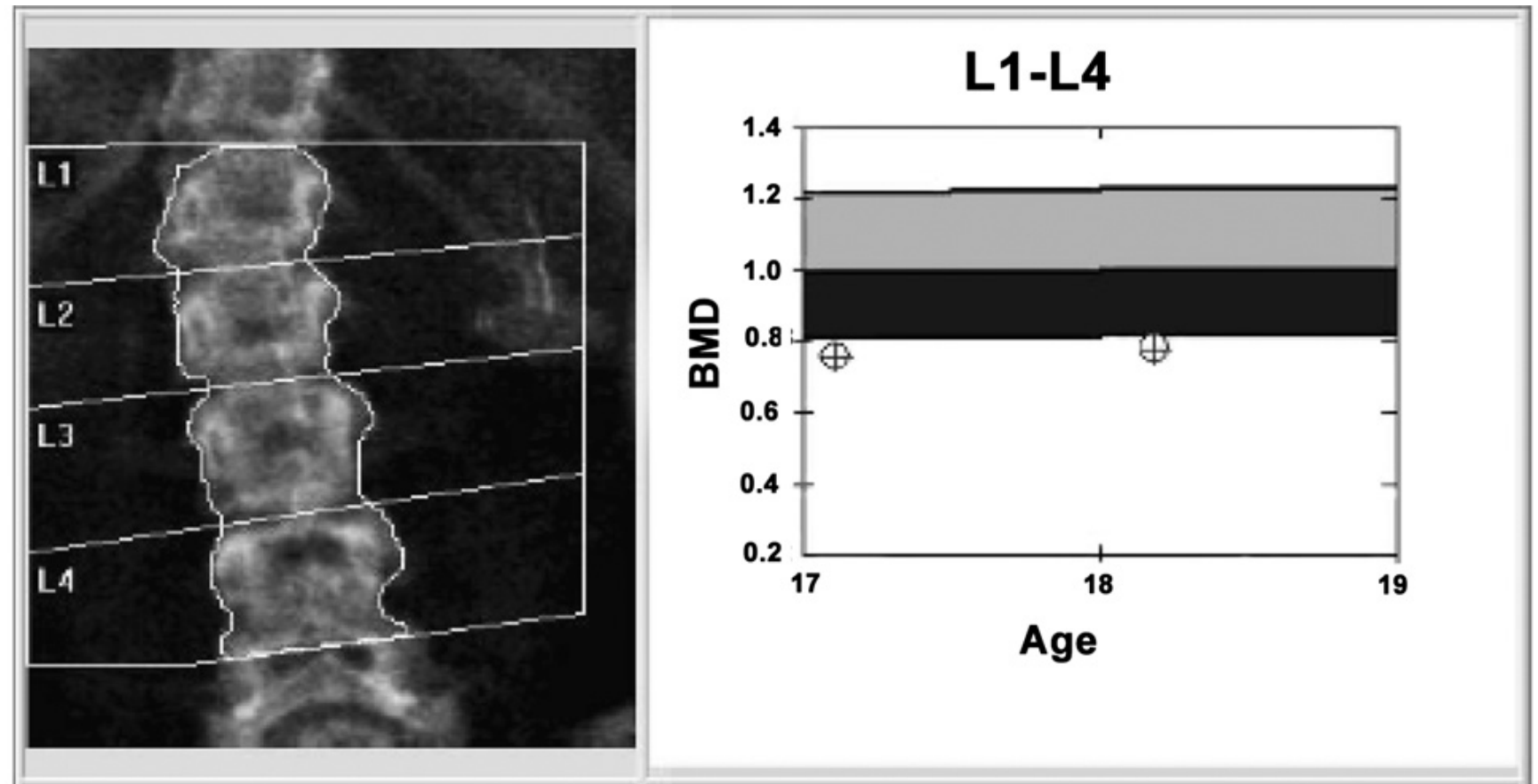
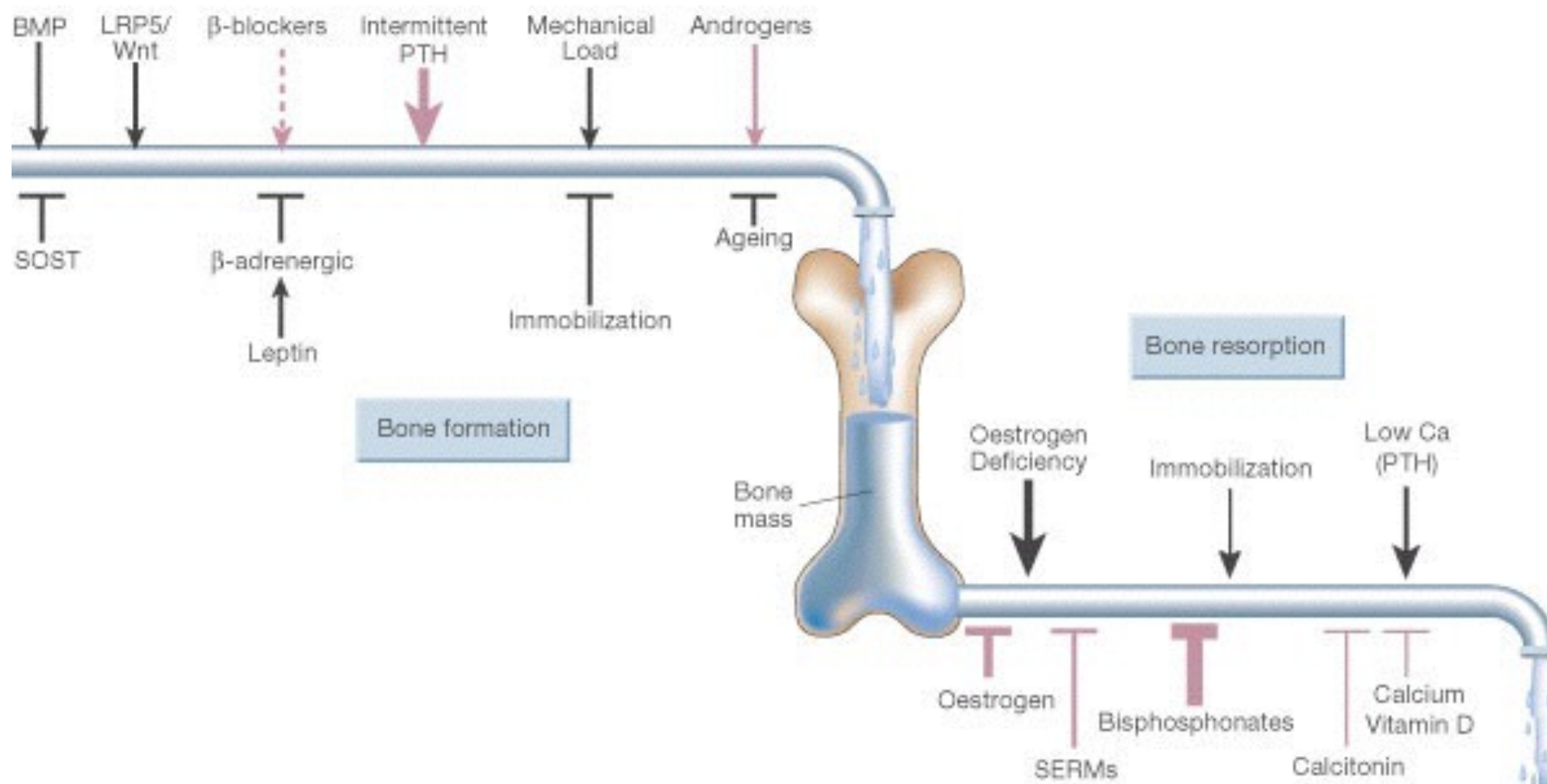
J Pediatr Health Care. (2012) *26*, 193-199.

Results Summary

Region	Area (cm²)	BMC (g)	BMD (g/ cm²)	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	8.16	5.75	0.705	77	-2.1	77
L2	7.96	6.14	0.771	76	-2.4	77
L3	9.85	8.13	0.825	79	-2.1	80
L4	10.60	8.44	0.796	76	-2.5	77
Total	36.57	28.46	0.778	77	-2.5	78

Total BMD CV 1.0%, ACF = 1.031, BCF = 1.016

Management

Shun-ichi Harada & Gideon A. Rodan, Nature 423:349-355, 2003

Management

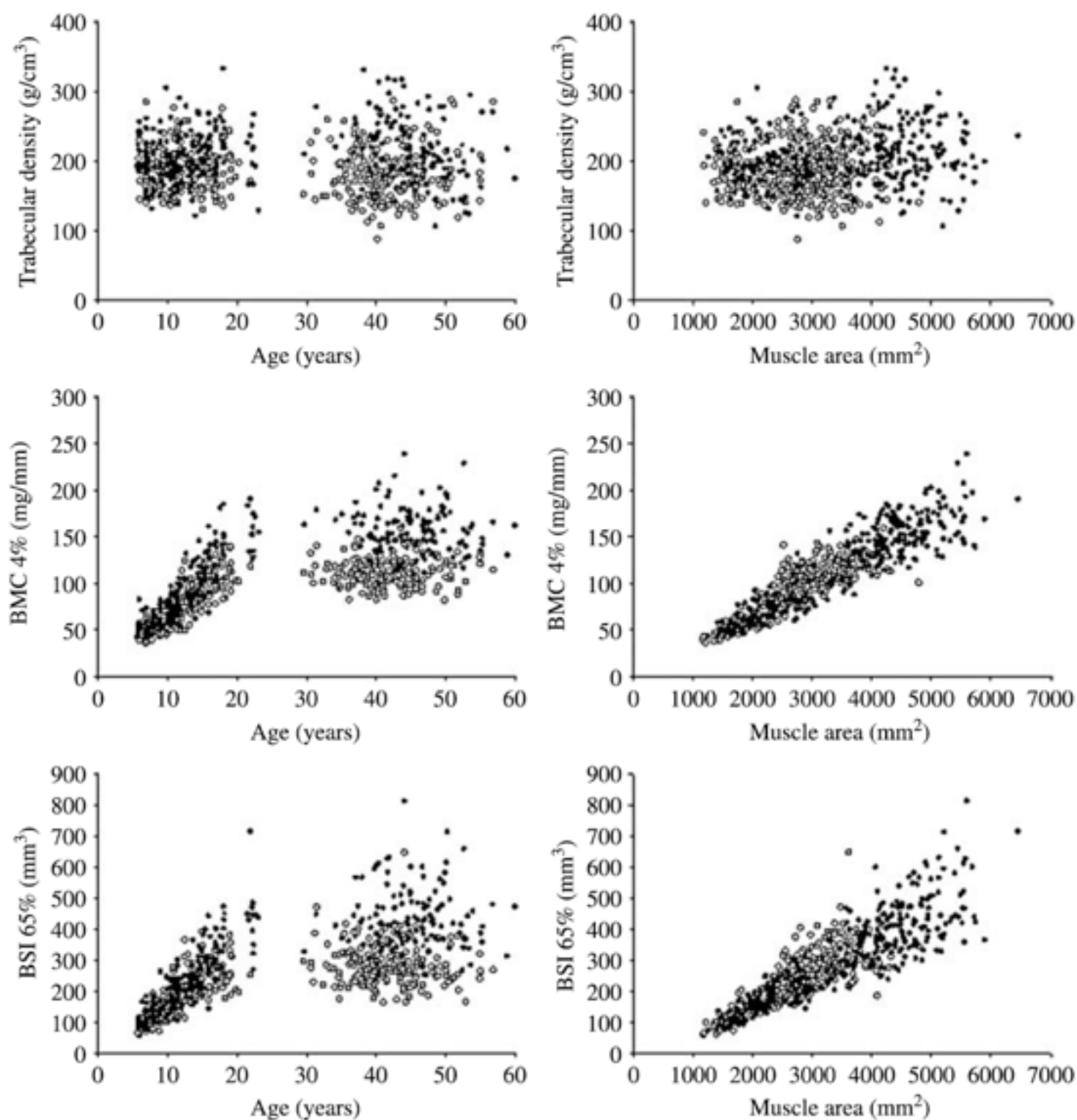
- Non-pharmacological interventions
  - Physical activity
  - Physiotherapy
  - Vitamin D
  - Calcium
- Pharmacological Intervention
  - Bisphosphonates

Physical activity

- Physical activity is crucial to bone health and an attempt should be made to increase bone loading and muscle strength in children with osteoporosis.
- Even short-term exercise intervention programmes have shown sustained effects on BMC in growing children.
- If adequate exercise is not possible due to the child’s physical condition, physiotherapy might prove useful.
- High-frequency, low-magnitude vibration increased bone mass and muscle strength in disabled children, and increased muscle force in patients with severe types of osteogenesis imperfecta.

European Journal of Endocrinology (2008) **159** S27–S31 ISSN 0804-4643

Mechanical influences on bone development in children

E Schoenau and O Fricke
Children's Hospital, University of Cologne, Kerpener Strasse 62, D-50924 Cologne, Germany
(Correspondence should be addressed to E Schoenau; Email: eckhard.schoenau@uk-koeln.de)

Sport e geometria ossea

- Durante la fase di crescita, l'attività sportiva stimola sia l'osso periostale che quello endocorticale
- Azione sede-specifica
    - (omero/periostale; femore endocorticale)
- Azione età-dipendente
    - Prepubere/periostale; pubere/endocorticale

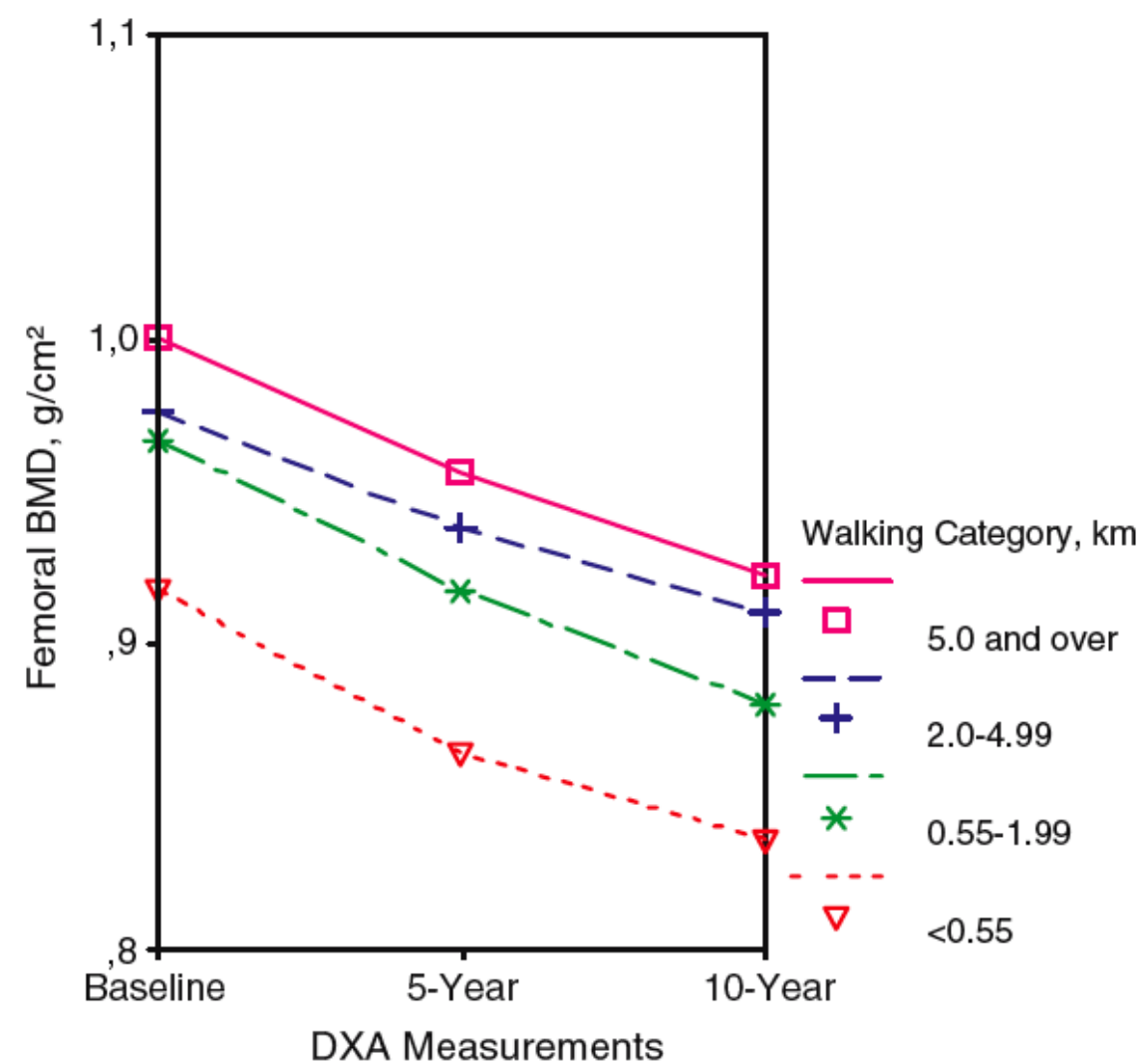
Esercizio fisico e sviluppo osseo

- L'effetto positivo dell'attività fisica sullo scheletro varia in relazione al tipo di esercizio ed al periodo di vita in cui viene effettuato
- Il maggior beneficio sia sulla densità minerale che sul volume osseo si verifica in epoca giovanile fino al raggiungimento del picco di massa ossea.
- Le attività che comportano elevato carico fisico (definite "weight bearing") sui vari segmenti ossei sono quelle che comportano i maggiori benefici scheletrici
- L'eccessiva attività fisica può comunque risultare estremamente dannosa per lo scheletro in accrescimento (i.e. alterazioni del ciclo mestruale, magrezza)

Eur J Appl Physiol (2006) 97: 509–515
DOI 10.1007/s00421-006-0208-7

ORIGINAL ARTICLE

Toni Rikkonen · Marjo Tuppurainen
Heikki Kröger · Jukka Jurvelin · Risto Honkanen

Distance of walking in childhood and femoral bone density in perimenopausal women

Clinical Rehabilitation 2008; **22:** 387–394

Results of a prospective pilot trial on mobility after whole body vibration in children and adolescents with osteogenesis imperfecta

Oliver Semler, **Oliver Fricke**, **Katharina Vezyroglou**, **Christina Stark**, **Angelika Stabrey** and **Eckhard Schoenau** Children's Hospital, University of Cologne, Cologne, Germany

Received 6th December 2006; returned for revisions 25th February 2007; revised manuscript accepted 3rd May 2007.

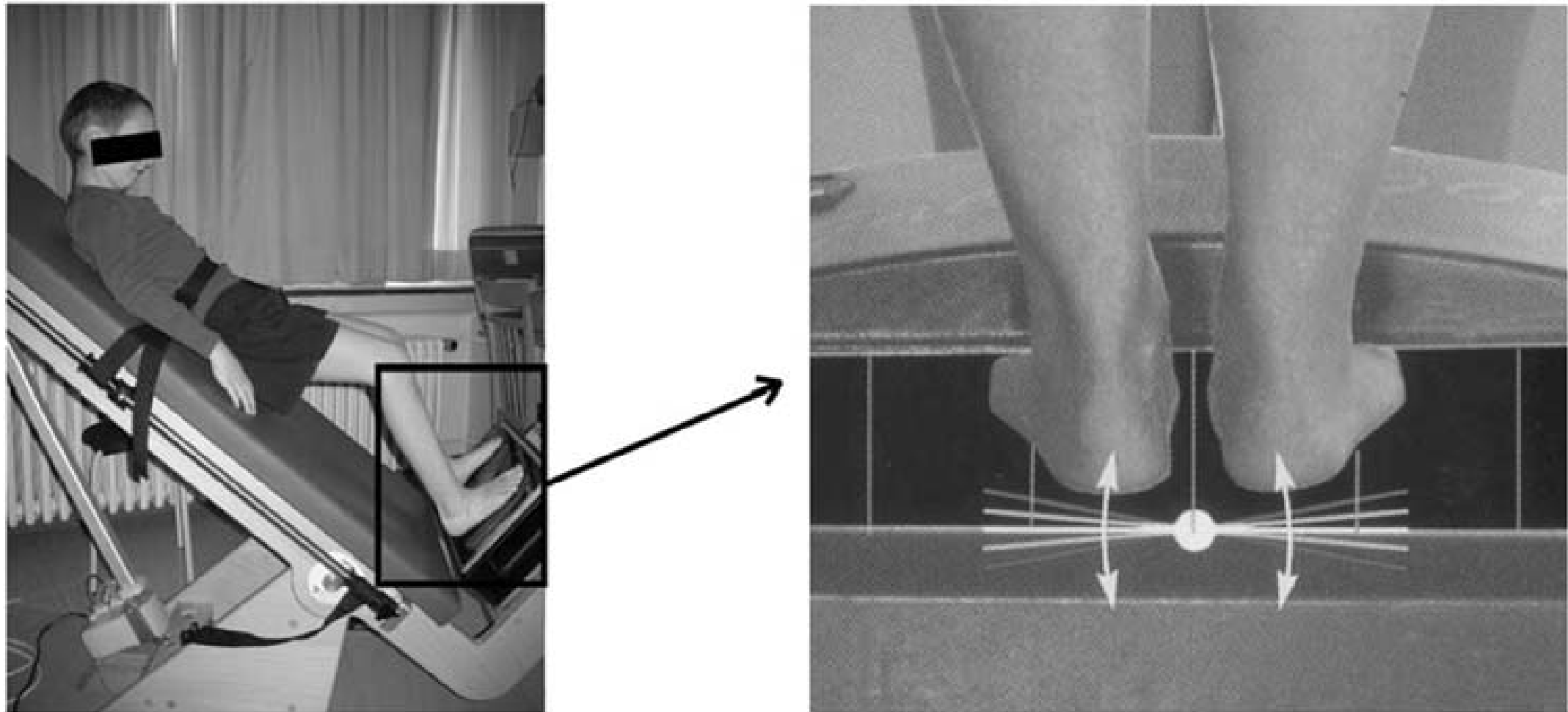



Figure 1 The Cologne Standing and Walking Trainer System Galileo.

Clinical Rehabilitation 2008; **22:** 387–394

Results of a prospective pilot trial on mobility after whole body vibration in children and adolescents with osteogenesis imperfecta

Oliver Semler, Oliver Fricke, Katharina Vezyroglou, Christina Stark, Angelika Stabrey and **Eckhard Schoenau** Children's Hospital, University of Cologne, Cologne, Germany

Received 6th December 2006; returned for revisions 25th February 2007; revised manuscript accepted 3rd May 2007.

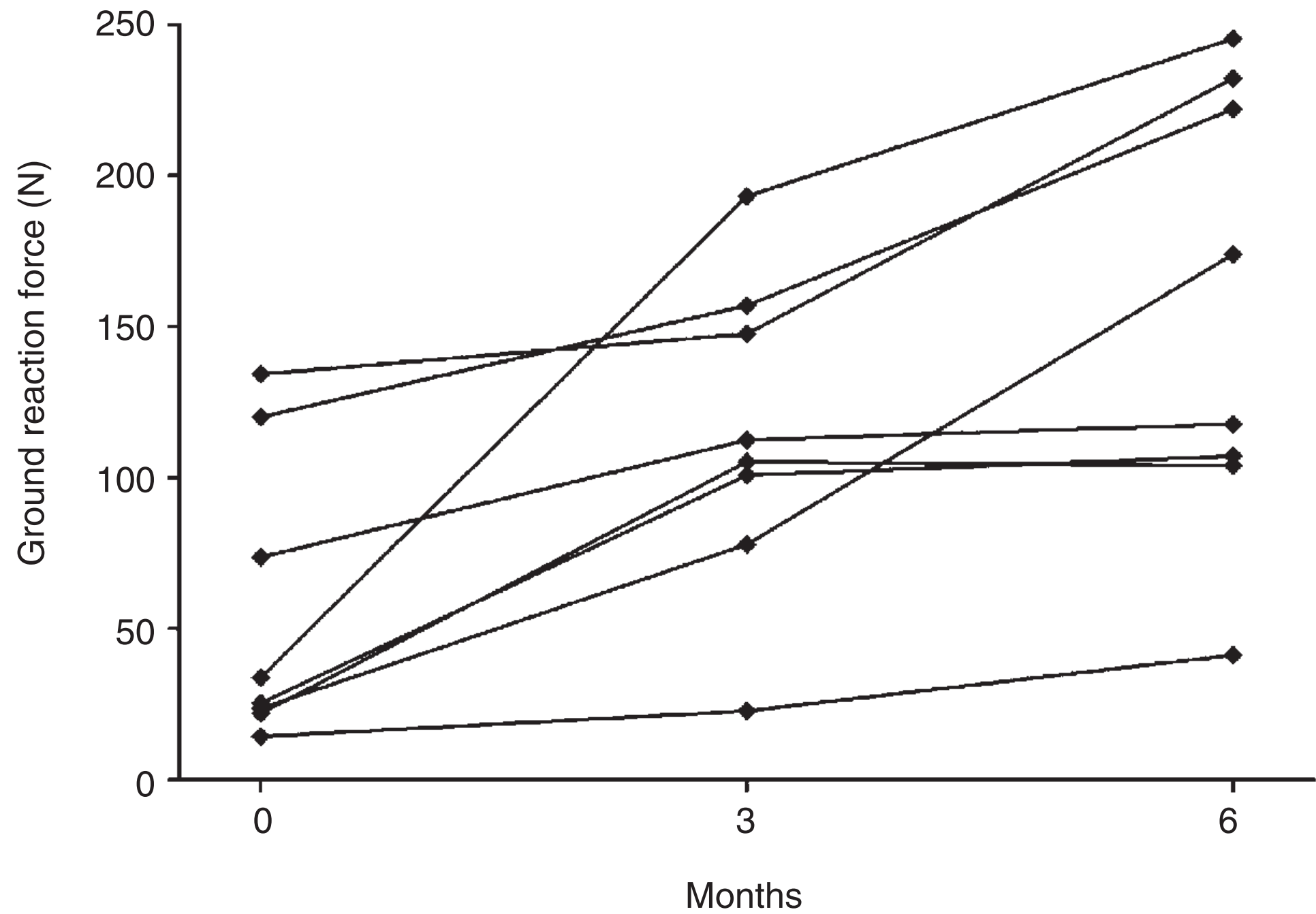



Figure 2 Changes of calculated ground reaction force during six months of whole body vibration.

Vitamin D

- Vitamin D deficiency should be identified and, where possible, corrected in all children with suspected osteoporosis.
- For optimal skeletal effects, serum levels as high as >80 nmol/l (>32 ng/ml) could be required.

- Vitamin D doses of up to 50 µg vitamin D_3 per day or 50,000 µg vitamin D_2 per week are effective in attaining serum 25(OH)D levels >80 nmol/l (>32 ng/ml) and are well-tolerated, as shown in patients with inflammatory bowel disease.

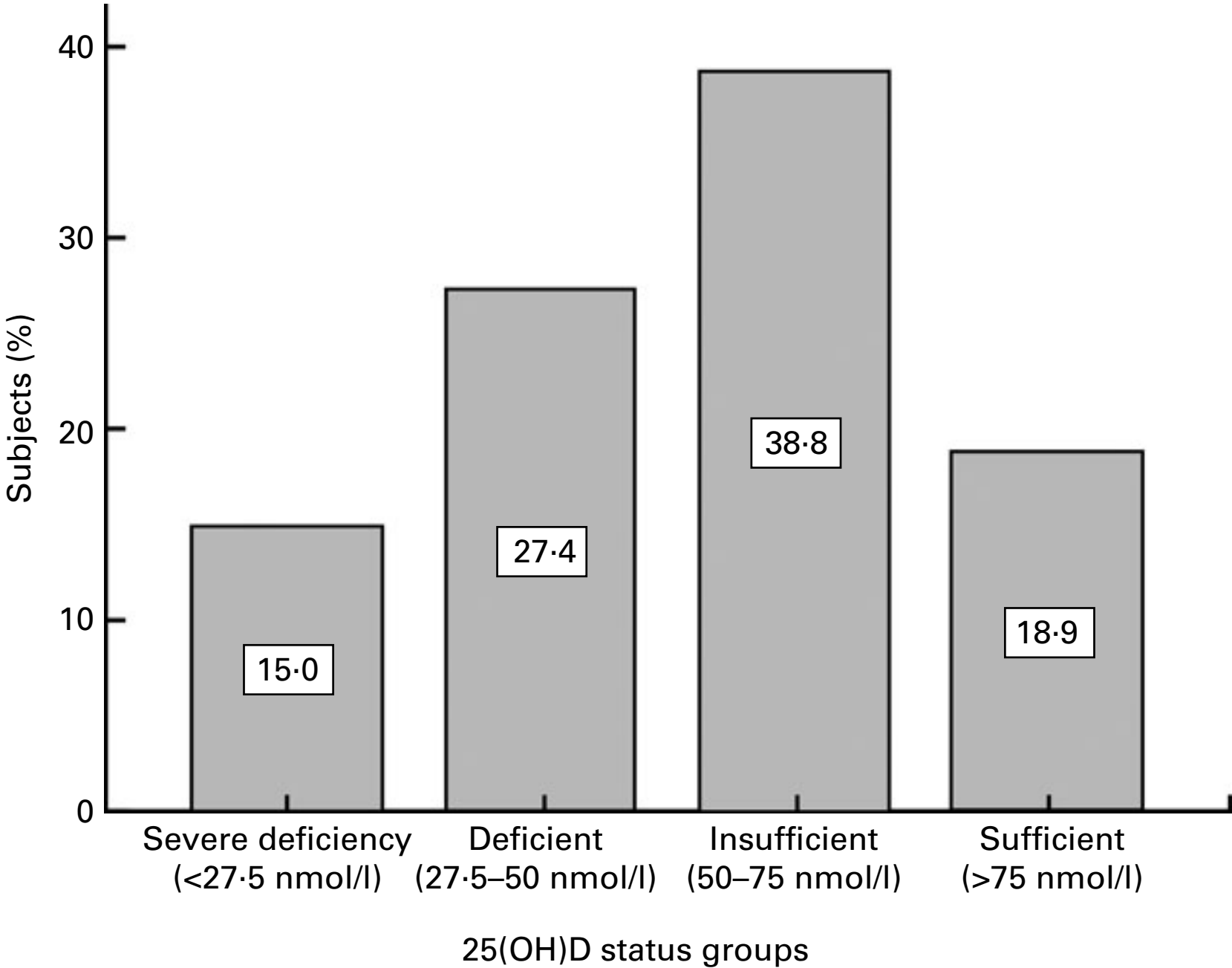
British Journal of Nutrition (2012), **107**, 755–764 doi:10.1017/S0007114511003527

Vitamin D status among adolescents in Europe: the Healthy Lifestyle in Europe by Nutrition in Adolescence study

Marcela González-Gross[1,2]*†, Jara Valtueña[1,3]†, Christina Breidenassel[2], Luis A. Moreno[4,5], Marika Ferrari[3], Matilde Kersting[6], Stefaan De Henauw[7], Frederic Gottrand[8], Elena Azzini[3], Kurt Widhalm[9], Anthony Kafatos[10], Yannis Manios[11] and Peter Stehle[2] on behalf of the HELENA Study Group

[1]*Department of Health and Human Performance, Faculty of Physical Activity and Sport Sciences (INEF), Universidad Politécnica de Madrid, C/Martín Fierro, 7, 28040 Madrid, Spain*
[2]*Institut für Ernährungs- und Lebensmittelwissenschaften – Humanernährung, Rheinische Friedrich-Wilhelms Universität, Bonn, Germany*
[3]*National Research Institute on Food and Nutrition, Rome, Italy*
[4]*Growth, Exercise, Nutrition and Development (GENUD) Research Group, Universidad de Zaragoza, Zaragoza, Spain*
[5]*Escuela Universitaria de Ciencias de la Salud, Universidad de Zaragoza, Zaragoza, Spain*
[6]*Research Institute of Child Nutrition Dortmund, Rheinische Friedrich-Wilhelms Universität, Bonn, Germany*
[7]*Department of Public Health, Ghent University, Ghent, Belgium*
[8]*Inserm U995, IFR114, University Lille 2, Lille, France*
[9]*Department of Paediatrics, Medical University of Vienna, Vienna, Austria*
[10]*Preventive Medicine and Nutrition Clinic, University of Crete School of Medicine, Iraclion, Crete, Greece*
[11]*Department of Nutrition and Dietetics, Harokopio University, Athens, Greece*

(Received 12 November 2010 – Revised 23 May 2011 – Accepted 31 May 2011 – First published online 17 August 2011)

2012 Gonza´lez-Gross Adolescents VitD

Condizioni a rischio di carenza di vitamina D

- Ridotta esposizione solare
  - eccessiva copertura con indumenti, polluzione atmosferica, istituzionalizzati
- Melanodermia
- Allattamento al seno senza profilassi
- Diete incongrue
  - soia, diete vegetariane, diete macrobiotiche
- Prematurità
- Nutrizione parenterale totale prolungata
- Malassorbimento intestinale cronico
- Epatopatie croniche
  - cirrosi biliare primitiva, atresia delle vie biliari
- Terapia cronica con anticonvulsivanti
  - fenobarbital, difenilidantoina, rifampicina, corticosteroidi
- Rachitismi genetici
  - ipofosfatemici, dipendente I e II

natural sunlight | fortified milk | cheese

butter/margarine | cereal | fish

Tabella 1. Alimenti contenenti vitamina D

Alimento	Contenuto di vitamina D (UI)
Latte vaccino	3-40/L
Latte fortificato/formule pediatriche	400/L
Burro	35/100 gr
Margarina	60/cucchiaino
Yogurt	89/100 gr
Formaggio parmigiano	28/100 gr
Formaggio Cheddar (dolce)	12/100 gr
Cereali fortificati	40/porzione
Funghi freschi	100/100 gr
Funghi essiccati	1.660/100 gr
Tuorlo d'uovo	20-25 per tuorlo
Gamberetti	152/100 gr
Tonno/sardine/salmone/sgombro sott'olio	224-332/100 gr
Salmone/sgombro cotti	345-360/100 gr
Aringa dell'Atlantico	1.628/100 gr
Olio di fegato di merluzzo	175/gr - 1.360/cucchiaino

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Tabella 4. **Fattori che modificano la sintesi cutanea di vitamina D**
• Quantità ed energia degli UV-B
• Latitudine
• Stagione
• Ora del giorno
• Atmosfera (nuvolosità, inquinamento), altitudine
• Quantità di superficie cutanea esposta
• Durata dell'esposizione
• *Indoor living*
• Utilizzo di filtri di sicurezza elevati
• Contenuto in melanina della pelle
• Tipo di abbigliamento
• Età > 50 anni
• Caratteristiche individuali (variazioni geneticamente determinate dell'attività del metabolismo della vitamina D)

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Solar UVB radiation

Dietary sources

Vitamin D

Macrophage

Maintenance of normal cell proliferation in prostate, colon, breast, etc.

Liver

Increased CD

M. tuberculosis

Death

VDR-RXR

Decreased p21, p27, etc.

25-OHase

VDR-RXR

Increased VDR mRNA, 1-OHase mRNA

Increased $1,25(OH)_2D$

Increased 1-OHase

25(OH)D

1-OHase

$1,25(OH)_2D$

TLR

LPS

Kidney

Decreased renin

1-OHase

$1,25(OH)_2D$

Activated T and B lymphocytes

Immune modulation

Pancreas

Increased insulin

Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

IBMS BoneKEy. 2011 April;8(4):178-186
http://www.bonekey-ibms.org/cgi/content/full/ibmske;8/4/178
doi: 10.1138/20110505

PERSPECTIVES

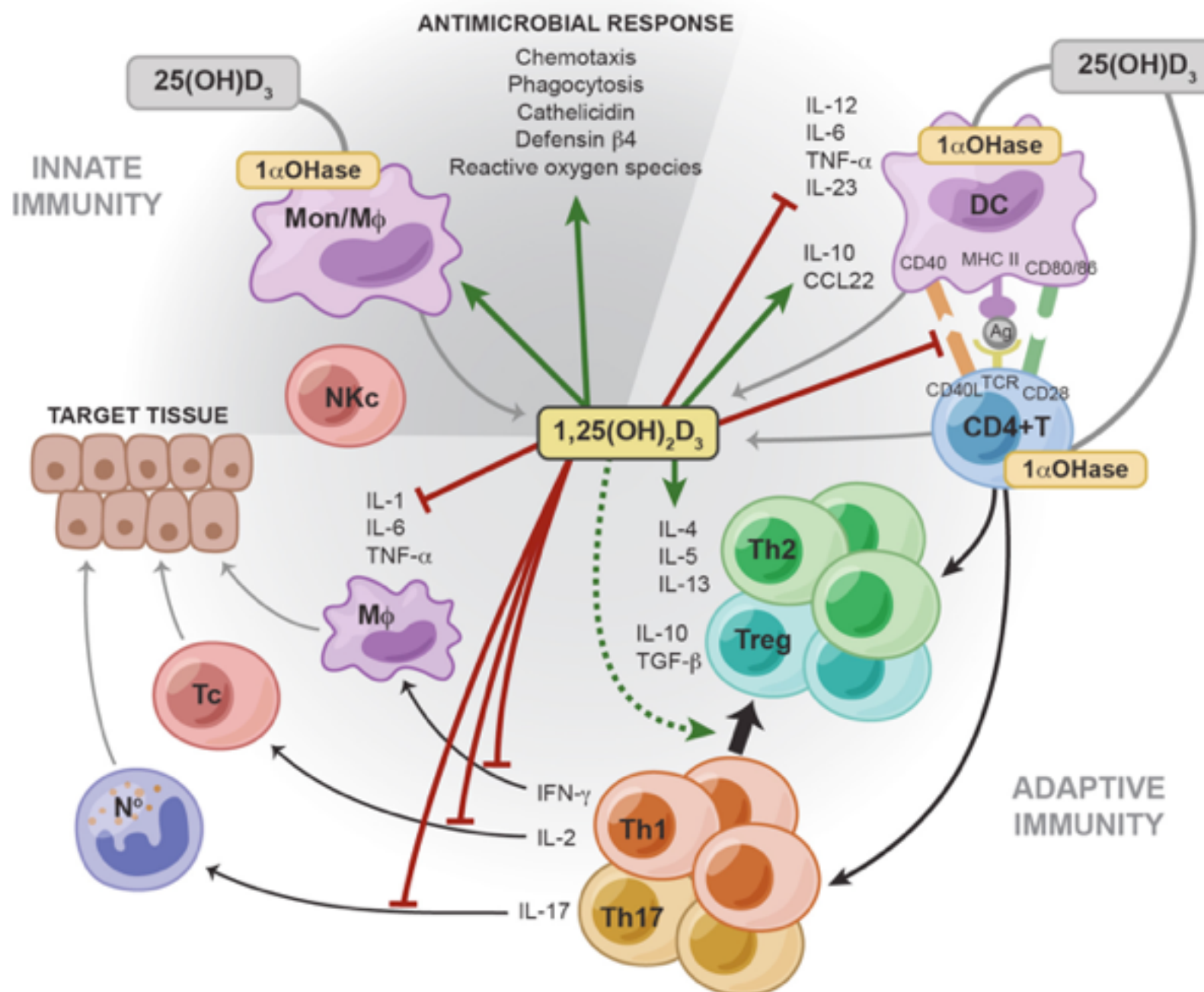
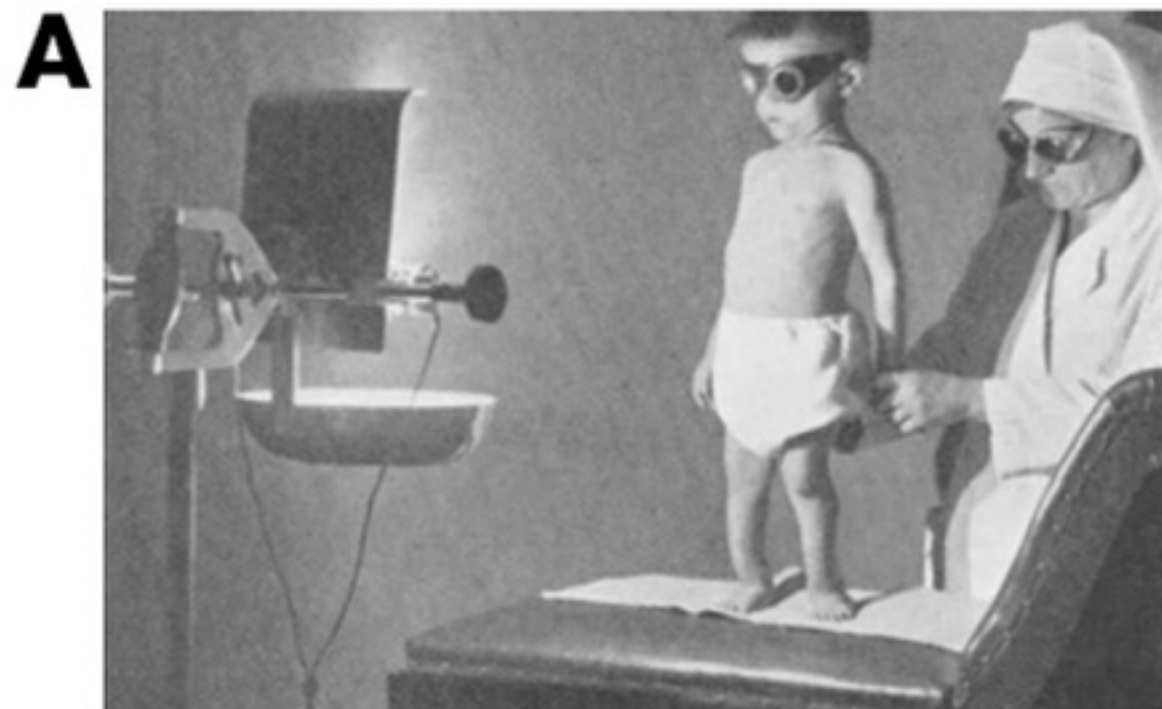
Vitamin D and the Immune System: Getting It Right

Chantal Mathieu

Laboratory of Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven (KUL), Leuven, Belgium

Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

A

B

Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

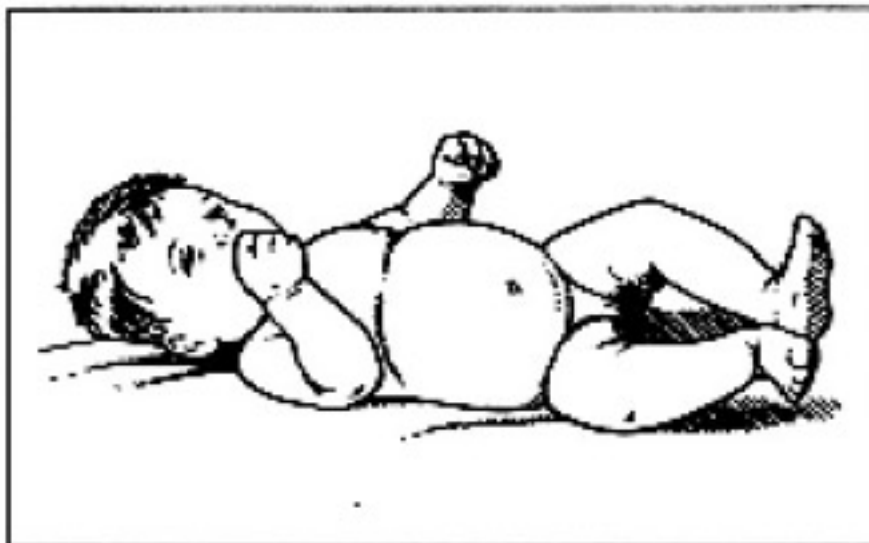
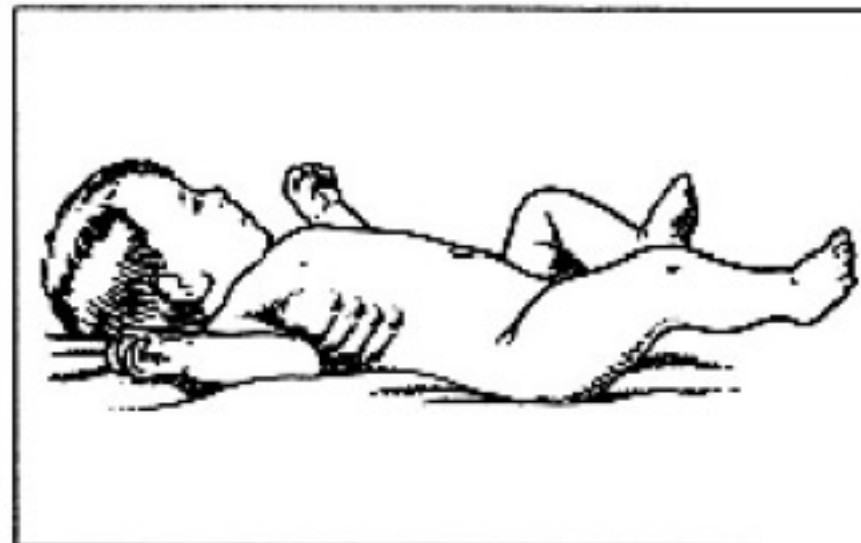
Rachitismo Carenziale

- Malattia dello scheletro nel periodo di più rapido accrescimento
- La causa è la carenza di vitamina D (e/o calcio)
  - Da insufficiente assunzione alimentare
  - Da insufficiente esposizione solare
- Ne consegue difetto di assorbimento intestinale di Ca e quindi diminuzione del prodotto Ca x P extracellulare indispensabile per la mineralizzazione
- Eccesso di tessuto osteoide non mineralizzato

Tabella 2. **Fattori predisponenti a una carenza di vitamina D**	
Meccanismo	**Cause**
Ridotta sintesi cutanea	Uso eccessivo di creme solari, pelle scura, età avanzata, stagione, latitudine e ora del giorno, pazienti con trapianto di cute post-ustioni con conseguente riduzione di 7-deidrocolesterolo.
Ridotta biodisponibilità	Fibrosi cistica, malattia celiaca, morbo di Whipple, morbo di Chron, chirurgia derivativa, farmaci che riducono l'assorbimento del colesterolo, abetalipoproteinemia, resezioni del piccolo intestino.
Aumentato catabolismo	Anticonvulsivanti, glucocorticoidi, HAART (trattamento AIDS), e farmaci antirigetto - che si legano allo steroide o al recettore dello xenobiotico o al pregnane X recettore.
Allattamento al seno	Esclusivo senza supplementazione
Ridotta sintesi di 25-idrossivitamina D	Epatopatia
Aumentata perdita urinaria di 25-idrossivitamina D	Sindrome nefrosica
Ridotta sintesi di 1,25-diidrossivitamina D	Insufficienza renale cronica
Ridotta disponibilità	Prematurità (scorte diminuite) Obesità (sequestro nel tessuto adiposo)
Altri disordini acquisiti	Osteomalacia indotta da tumori, iperparatiroidismo primario, disordini granulomatosi, sarcoidosi, tubercolosi, ipertiroidismo
Aumentato fabbisogno	Velocità di crescita ossea aumentata

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Tabella 6.	Principali segni clinici di rachitismo
SEGNI GENERALI	• Basso peso alla nascita • Deficit di accrescimento staturo-ponderale • Odore ammoniacale dei panni • Sudorazione • Capelli usurati alla nuca • Anemia • Convulsioni ipocalcemiche • Letargia • Irritabilità • Miopatia prossimale • Deficit muscolo-legamentoso • Ipotonia • Ritardo acquisizioni motorie • Grosso addome • Insufficienza respiratoria (da demineralizzazione ossea costale della gabbia toracica) • Laringospasmo • Predisposizione alle infezioni respiratorie • Mielofibrosi • Sindrome di Von Jacksch-Luzet, rara e propria delle forme gravi: anemia, splenomegalia, pseudoleucemia mieloide cronica, midollo osseo ipoplasico, eritropoiesi epatosplenica compensatoria
SEGNI OSSEI	• Tumefazione o collaretto epifisario (polsi, ginocchia, malleoli): da ipertrofia della zona di maturazione e accumulo di tessuto osteoide nelle cartilagini di coniugazione • Deformità arti inferiori (*genu* varum o *valgum*) • Fratture spontanee: in genere indolori e senza spostamento • Craniomalacia • Ritardo di chiusura della fontanella • Bozze frontali (e parietali) sporgenti • Deformazioni del cranio (*caput quadratum* o natiforme), asimmetrie • Rosario rachitico • Deformazioni toraciche (torace carenato, solco di Harrison) • Cifosi, scoliosi • Inversione della lordosi cervico-dorsale o lombare • Coxa vara o valga • Alterazioni dei diametri del bacino • Alterazioni dentarie (ritardo della dentizione, alterato ordine di comparsa dei denti, difetto dello smalto, carie precoci)

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

. Solco di Harrison.

. Rosario rachitico.

. Gibbo rachitico, ben evidente nella posizione seduta.

Rachitismo - diagnosi

- Segni Clinici:
  - Ritardo chiusura fontanella
  - Varismo ginocchia
- Rx mano e polso
- Ca, P, ALP, PTH, 25-OH-D

Segni biochimici delle principali forme di rachitismo

Patologia	*Calcio*	*Fosfato*	*ALP*	*PTH*	*25-OH-D*	*1,25(OH)$_2$D*
Rachitismo carenziale	N o ↓	N o ↓	↑	↑	N o ↓	N o ↓ o ↑
R da malassorbimento intestinale cr	N o ↓	N o ↓	↑	↑	N o ↓	N o ↓ o ↑
R nelle malattie epato-biliari	N o ↓	N o ↓	↑	↑	N o ↓	↓
R da anticonvulsivanti	N o ↓	N o ↓	↑	↑	↓	N o ↓
R ipofosfatemico familiare	N	↓	↑	N	N	N o ↓*
R vitamina D-dipendente tipo I	↓	↓	↑	↑	N o ↑	↓
R vitamina D-dipendente tipo II	↓	↓	↑	↑	N o ↑	↑

* normali in termini numerici ma inappropriatamente ridotti rispetto all'ipofosfatemia

da Saggese G., Baroncelli GI.
I Disturbi del Metabolismo fosfo-calcico.
In Endocrinologia Pediatrica, McGraw Hill, 2001

Tabella 5. Forme di rachitismo

Da alterato apporto di vitamina D

- Rachitismo carenziale
- Rachitismo da malassorbimento intestinale cronico

Da alterato metabolismo epatico della vitamina D

- Rachitismo nelle malattie epato-biliari (osteodistrofia epatica)
- Rachitismo da trattamento cronico con farmaci anticonvulsivanti

Da alterato metabolismo renale della vitamina D

- Osteodistrofia renale
- Rachitismo da tubulopatie
- Rachitismo oncogenetico
- Rachitismo ipofosfatemico familiare
  - AD per mutazione del gene per l'FGF23
  - X-linked, in cui è mutato il gene PHEX.
- Rachitismo vitamina D dipendente tipo I: mutazione del gene CYP27B1 per la 25-idrossivitamina D-1α idrossilasi renale

Da ridotta azione della vitamina D

- Rachitismo vitamina D dipendente tipo II: mutazione del gene per il recettore della vitamina D - VDR
- Rachitismo vitamina D dipendente di tipo III: iperproduzione delle proteine leganti l'elemento responsivo all'ormone

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Moumou A. 2 aa 2 mm

Moumou A. 2 aa 9 mm, dopo 6 m terapia

Moumou A. 2 aa 2 mm

Moumou A. 2 aa 9 mm, dopo 6 m terapia

Table 2

Vitamin D status and associated biochemistries: serum levels of 25(OH)D, $1,25(OH)_2D$, Ca, HPO_4^{2-}, alkaline phosphatase (Alk. phos.), PTH, and FGF23

	25(OH) D, ng/ml	1,25(OH)2D	Ca	HPO_4^{2-}	Alk. phos.	PTH	FGF23	Skeletal disease
Vitamin D deficiency	<20	↑	↓ NL	↓	↑	↑	NL	Rickets/osteomalacia
Vitamin D insufficiency	21–29	↑ or NL	NL	NL	↑ or NL	↑ or NL	NL	↓ BMD
Vitamin D sufficiency	>30	NL	NL	NL	NL	NL	NL	None
XLH	NL	↓	NL	↓↓	↑	NL	↑ or NL	Rickets
ADHR	NL	↓	NL	↓↓	↑	NL	↑↑	Rickets
TIO	NL	↓	NL	↓↓	↑	NL	↑↑	Rickets

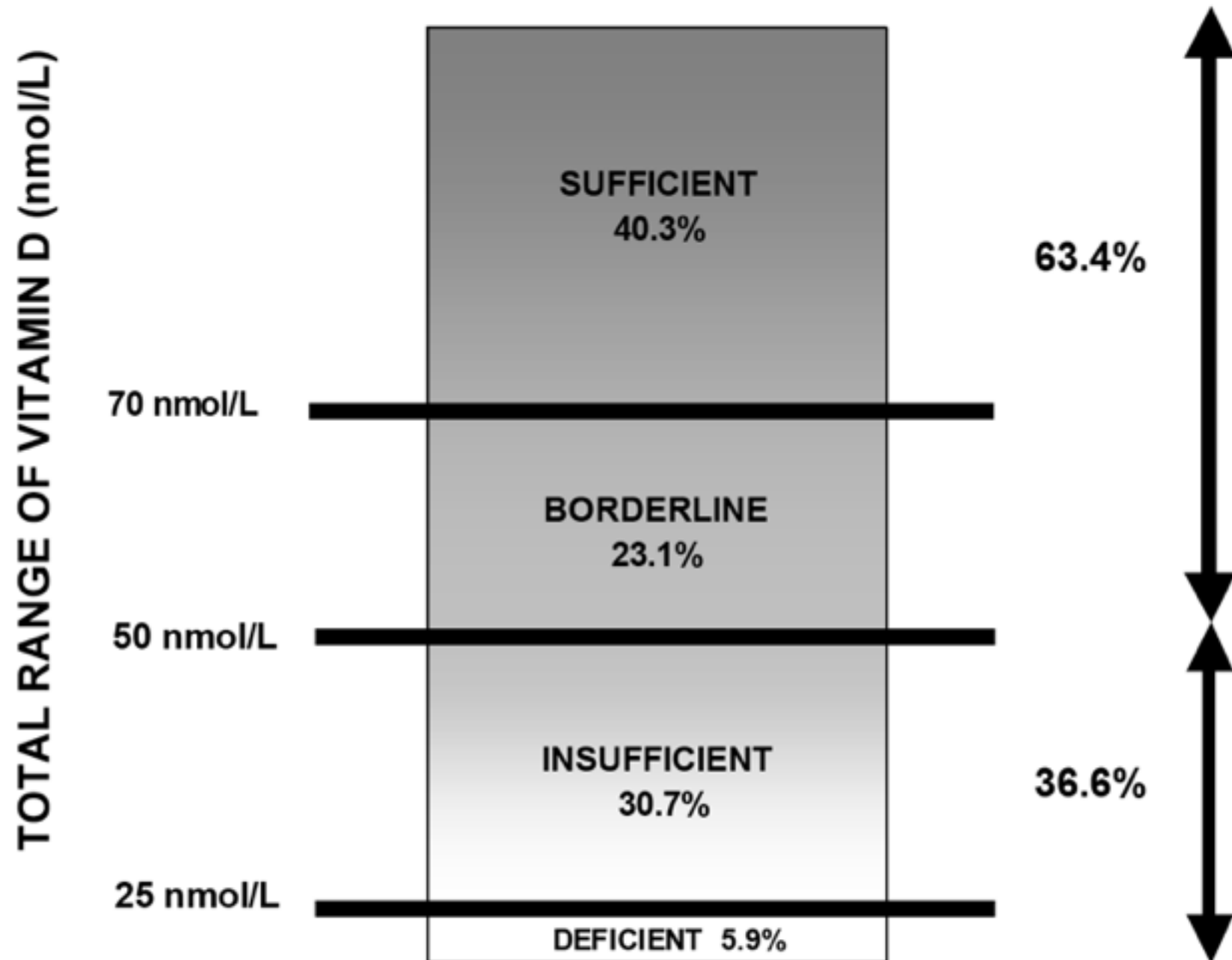
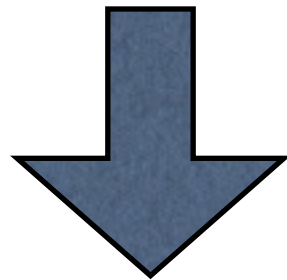
The upward-pointing arrows (↑ and ↑↑) indicate that the level is moderately or markedly above the normal range, respectively, and the downward-pointing arrows (↓ and ↓↓) indicate that the serum level is moderately or markedly below the normal range, respectively. NL represents levels within the normal range. BMD, bone mineral density; XLH, X-linked hypophosphatemic rickets; ADHR, autosomal dominant hypophosphatemic rickets; TIO, tumor-induced osteomalacia.

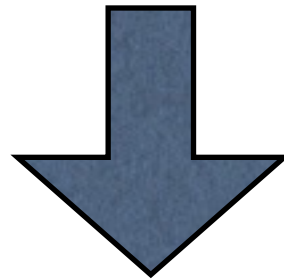
Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

Tabella 7. Popolazioni a rischio di carenza di vitamina D

- Obesi (vitamina D sequestrata nel tessuto adiposo e meno disponibile per il resto del corpo)
- Pazienti anziani (minore facilità di sintesi e utilizzo della vitamina D)
- Farmaci (anticonvulsivanti, antitubercolari, glucocorticoidi, *highly active antiretroviral therapy* (HAART)
- Alterazioni intestinali (interferenza con l'assorbimento dei grassi e vitamina D
- Prematuri (ridotte scorte)
- Pazienti con diete deficitarie (vegetariane, macrobiotiche)
- Pazienti in Nutrizione Parenterale Totale (TPN)
- Pazienti epatopatici (ridotta sintesi di 25OH vitamina D)
- Pazienti nefropatici (ridotta sintesi 1,25$(OH)_2$vitamina D
- Disordini ereditari associati a deficit di vitamina D
- Pazienti con melanodermia

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

MATERNAL VITAMIN D CONCENTRATION
N = 424
TOTAL RANGE OF VITAMIN D (nmol/L)
SUFFICIENT
40.3%
63.4%
70 nmol/L
BORDERLINE
23.1%
50 nmol/L
INSUFFICIENT
30.7%
36.6%
25 nmol/L
DEFICIENT 5.9%

Vitamina D ≠ Vitamina per la crescita e l'osso

funzioni extra ossee

Vitamina D $\neq$ Vitamina per i bambini

vita adulta e senile

gravidanza

Tabella 3. Livelli di deficit, normalità ed eccesso di vitamina D in base ai valori ematici di 25(OH)D

Classificazione	Livelli di 25(OH)D
Deficit molto grave	<12,5 nmol/L (<5 ng/mL)
Deficit grave	12,5-25,0 nmol/L (5-10 ng/mL)
Deficit moderato	25,0-50,0 nmol/L (10-20 ng/mL)
Normalità	50,0-250 nmol/L (20-100 ng/mL)
Valore desiderato	**>75,0 nmol/L (>30 ng/mL)**
Eccesso	>250 nmol/L (>100 ng/mL)
Intossicazione	>375 nmol/L (>150 ng/mL)

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Tabella 7.	Popolazioni a rischio di carenza di vitamina D

- Obesi (vitamina D sequestrata nel tessuto adiposo e meno disponibile per il resto del corpo)
- Pazienti anziani (minore facilità di sintesi e utilizzo della vitamina D)
- Farmaci (anticonvulsivanti, antitubercolari, glucocorticoidi, *highly active antiretroviral therapy* (HAART)
- Alterazioni intestinali (interferenza con l'assorbimento dei grassi e vitamina D
- Prematuri (ridotte scorte)
- Pazienti con diete deficitarie (vegetariane, macrobiotiche)
- Pazienti in Nutrizione Parenterale Totale (TPN)
- Pazienti epatopatici (ridotta sintesi di 25OH vitamina D)
- Pazienti nefropatici (ridotta sintesi 1,25$(OH)_2$vitamina D
- Disordini ereditari associati a deficit di vitamina D
- Pazienti con melanodermia

Antoniazzi F et al. Il deficit di vitamina D in età evolutiva.
Informer in Endocrinologia, Hippocrates 2010

Calcium

- Inadequate intake or increased loss of calcium and protein should be corrected with dietary modifications or supplements. The effectiveness of supplemental calcium (at doses exceeding the age-specific recommended daily intake) in improving bone mass has been questioned. Some studies have indicated positive effects on bone mass in children whereas a meta-analysis of calcium supple- mentation trials found only a small effect of calcium sup- plementation on BMD in healthy children; this effect is too small to result in clinical benefits in terms of reduced fracture risk in the general population. Whether supplementation would have a beneficial effect on BMD in chronically ill children remains unclear. Calcium supplements have recently been associated with increased risk of cardiovascular events in adults and therefore bolus administration (as with supplemental tablets) is discouraged; ideally calcium should be obtained from an appropriately balanced diet

Nutrition, Metabolism & Cardiovascular Diseases (2011) 21, 922—932

available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/nmcd
Nutrition, Metabolism & Cardiovascular Diseases

The third Italian National Food Consumption Survey, INRAN-SCAI 2005—06 — Part 1: Nutrient intakes in Italy

S. Sette*, C. Le Donne, R. Piccinelli, D. Arcella, A. Turrini, C. Leclercq, On Behalf of the INRAN-SCAI 2005—06 Study Group[1]

GRUPPO DI ETA'	ANNI	MG/DIE
Neonati/bambini	0-10	400-1200
Adolescenti/giovani adulti	11-24	1200-1500
Donne	Premenopausa	1000
	Gravidanza/allattam.	1200-1550
	Oltre 65 anni	1500
Uomini	25-65	1000
	Oltre 65	1500

INTAKE DI CALCIO

ETÀ	0-3	3-10	10-18M	10-18F	18-65M	18-65F	>65M	>65F
PERCENTILI								
5°	247	407	420	418	335	334	377	326
50°	669	714	848	759	756	697	778	735
95°	1070	1197	1435	1306	1433	1233	1403	1285

Ridotto apporto di calcio

- intolleranza al lattosio
- atopia
- intolleranza alle PLV
- non assunzione di formule di proseguimento

- Optimizing modifiable extrinsic factors such as calcium, vitamin D, and exercise may be effective in milder cases of osteoporosis. However, there are clinical circumstances when conservative measures are inadequate and pharmacologic treatment is necessary.

- A general conceptual approach to treat osteoporosis is either to stimulate new bone formation or prohibit bone resorption. Currently, teriparatide is the only available treatment with anabolic actions on bone. There are lingering safety concerns though, of bone neoplasia in children with open epiphyses. A black box warning has been issued to caution against the use of teriparatide in pediatric patients.

Pharmacologic Treatment

Shun-ichi Harada & Gideon A. Rodan, Nature 423:349-355, 2003

Published in final edited form as:
Mo Med. 2011 ; 108(2): 118–123.

The Pharmacological Management of Osteoporosis

Amy E. Riek, MD and
Clinical Fellow in the Division of Endocrinology, Metabolism, and Lipid Research at Washington University in St. Louis

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Professor of Medicine in the Division of Endocrinology, Metabolism, and Lipid Research at Washington University in St. Louis

Amy E. Riek: ariek@dom.wustl.edu; Dwight A. Towler: dtowler@dom.wustl.edu

2011 Riek Osteoporosis Treatment

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Amy E. Riek: ariek@dom.wustl.edu; Dwight A. Towler: dtowler@dom.wustl.edu

Targeting The Osteoblast in Osteoporosis

Causes, mechanisms and management
of paediatric osteoporosis
Outi Mäkitie
NATURE REVIEWS | RHEUMATOLOGY

Table 2 Pharmacological agents used for the treatment of osteoporosis (in adults)

Agent		Mechanism of action	Experience in paediatric populations
Oestrogen or oestrogen with progestogen	X	Delays age-related bone loss in postmenopausal women	Used in adolescent girls with paediatric osteoporosis and hypogonadism, delayed puberty or amenorrhoea[49,124]
Testosterone	X	Prevents bone loss in men with age-related hypogonadism	Used in adolescent boys with paediatric osteoporosis and hypogonadism or delayed puberty[51,125]
Growth hormone	?	Increases bone formation rate, improves muscle mass, alters mineral metabolism by increasing renal phosphate reabsorption	Used in children and adolescents with growth hormone deficiency; efficacy in paediatric patients with glucocorticoid-induced osteoporosis has not been established[47,126]
Selective oestrogen receptor modulators	X	Oestrogen-like action that selectively targets bone	Cannot be used in paediatric osteoporosis
Teriparatide	??	Recombinant human parathyroid hormone; stimulates bone formation when used intermittently (as daily injections)	Contraindicated in children; osteosarcoma observed in young rats in preclinical studies. Has been successfully used in some children to treat hypoparathyroidism[127]
Strontium ranelate	X	Increases bone formation and decreases bone resorption	No experience in paediatric populations
Bisphosphonate		Prevents attachment of osteoclasts to bone surface; inhibits bone resorption and promotes osteoclast apoptosis	Bisphosphonates (especially intravenous pamidronate, intravenous zoledronic acid and oral alendronate) have been used to treat moderate-to-severe primary osteoporosis caused by osteogenesis imperfecta Increased BMD but limited evidence of fracture prevention Variable efficacy in fibrous dysplasia Little experience in paediatric secondary osteoporosis[110,115]
Denosumab	??	Monoclonal anti-RANKL antibody that prevents interaction of RANKL with its receptor on osteoclasts and osteoclast precursors; inhibits osteoclast-mediated bone resorption	One case report describing use in severe polyostotic fibrous dysplasia: effective control of fibrous dysplasia but substantial mineral homeostatic disturbances during and after treatment[128]
Calcitonin	X	Decreases osteoclast activity	Inferior efficacy to bisphosphonates. Has been used to control acute pain after osteoporotic fracture. Linked to increased cancer risk in adults and should not be used to treat paediatric osteoporosis[129]

Abbreviations: BMD, bone mineral density; RANKL, receptor activator of NFκB ligand

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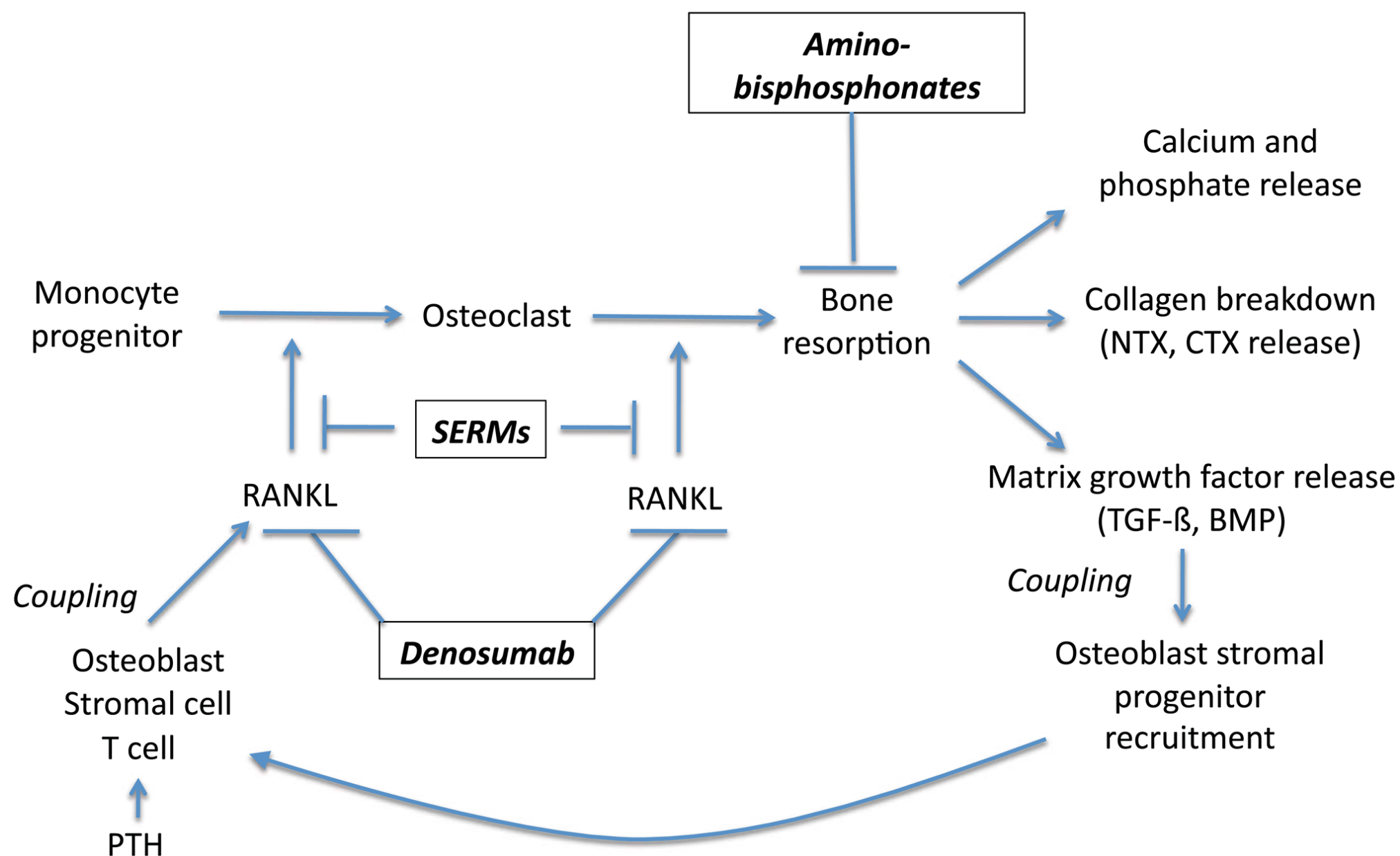
Bisphosponates

LAL

18/05/00

22/06/00

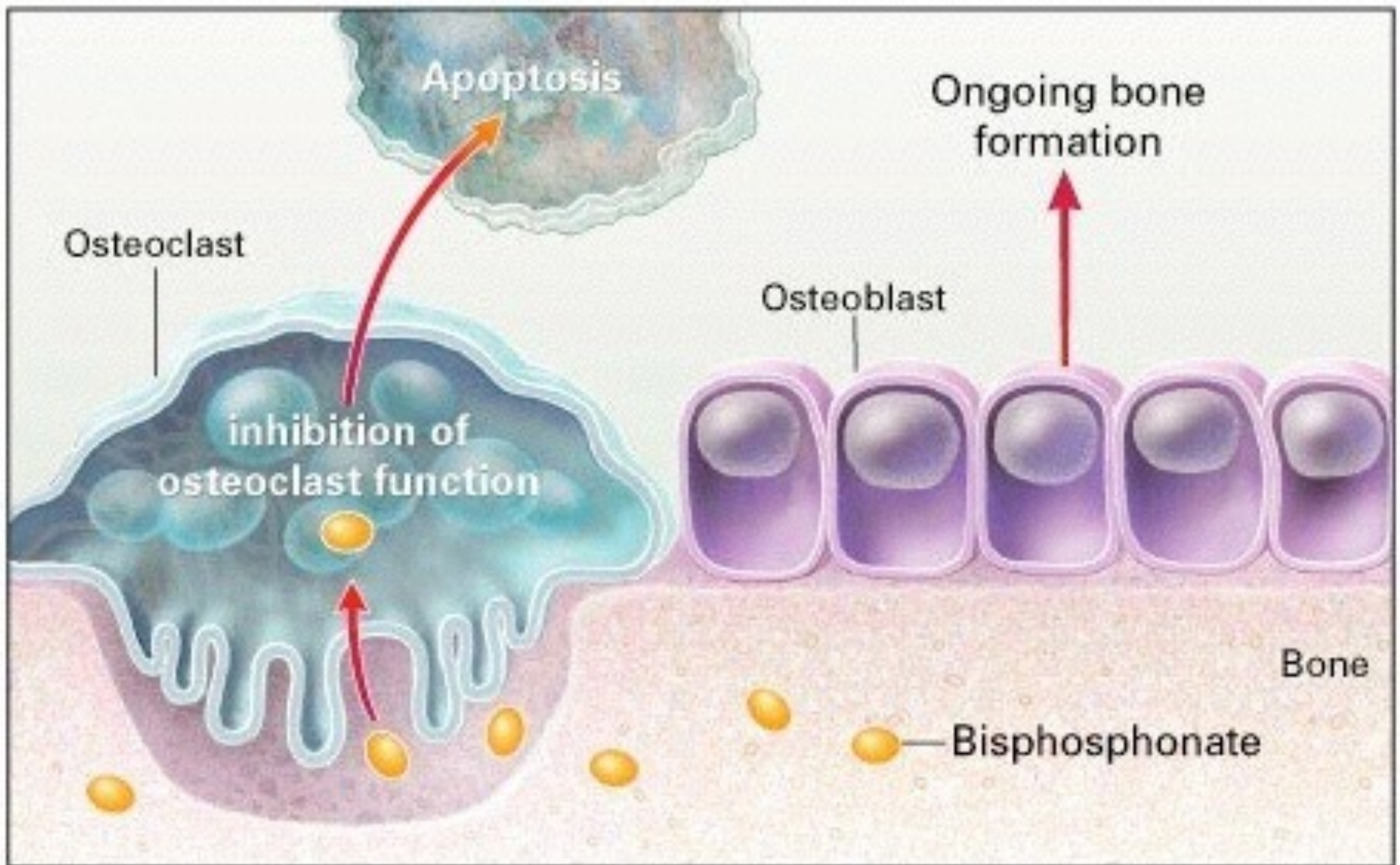
04/10/00

Diagnosi e terapia dell'osteoporosi in età evolutiva

Tabella 4. Utilizzo dei bisfosfonati in età evolutiva

Patologia primitiva dell'osso	Osteogenesi imperfetta	
	Osteoporosi idiopatica giovanile	
	Displasia Fibrosa- Sindrome di McCune-Albright	
	Morbo di Paget giovanile	
Patologia secondaria dell'osso	Condizioni associate a osteoporosi generalizzata da farmaci, immobilità, talassemia, fibrosi cistica ecc.)	
	Malattia di Gaucher	
	Algodistrofia	
	Lesioni ossee da sindrome SAPHO (*Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis*)	
	Lesioni ossee da mucolipidosi	
	Lesioni ossee da malattia di Menkes	
	Sindrome di Hadju-Cheney	
	Malattie calcificanti	Miosite ossificante primitiva
		Calcificazioni arteriose giovanili
		Ossificazioni ectopiche post-trauma cerebrale
		Dermatomiosite
		Ossalosi
	Condizioni di ipercalcemia	Leucemie e tumori solidi
		Iperparatiroidismo
		Steatonecrosi nel neonato
		Immobilizzazione
		Idiopatica

Antoniazzi F.
Informer in Endocrinologia, 2010; 13: 6-13

Solomon CG N Engl J Med, 346, No. 9 February 28, 2002

Bone metabolism

- Bone apposition markers

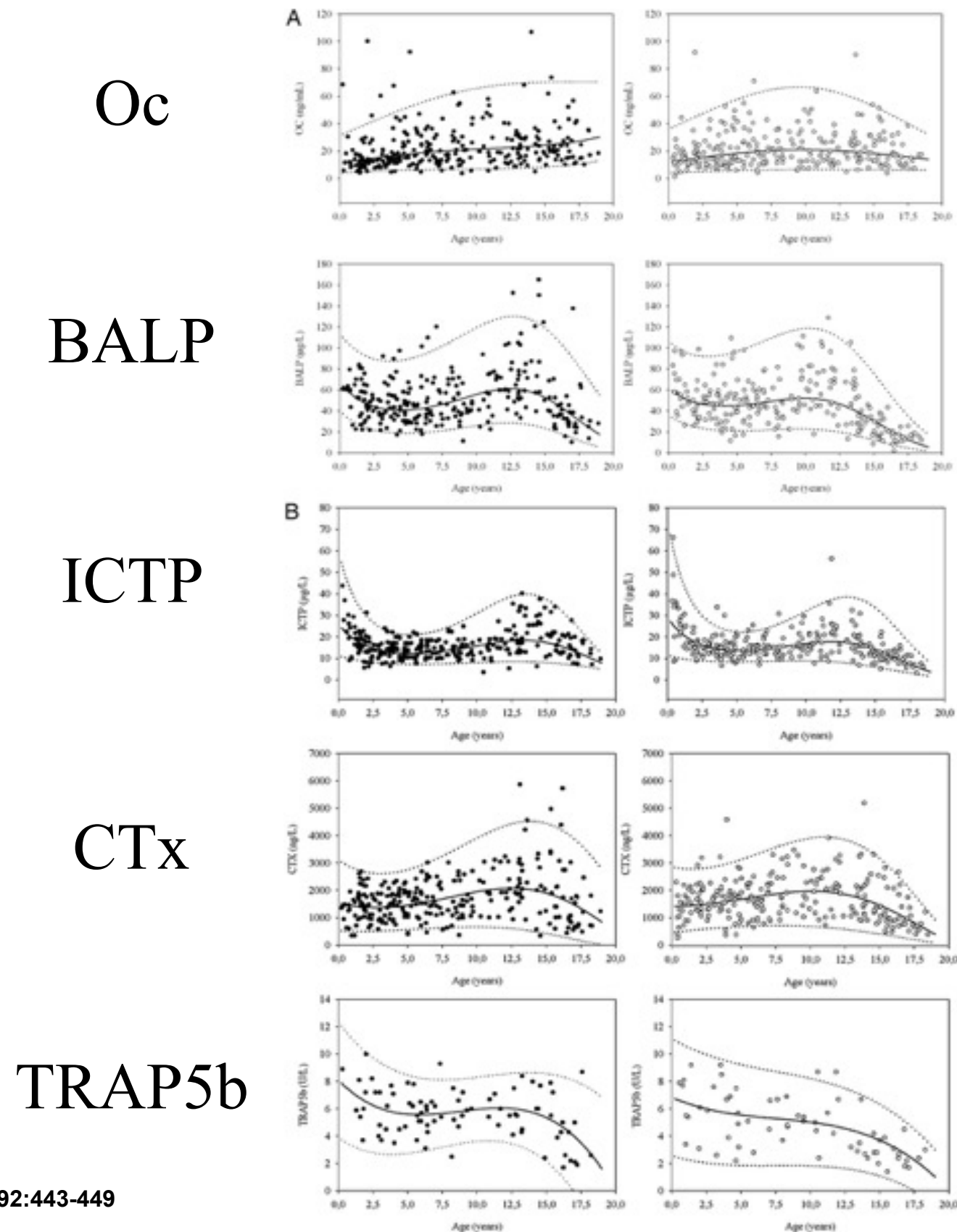
  Bone ALP, osteocalcin (OC), undercarboxylated osteocalcin (ucOC), procollagen type I C- e N-terminal peptides (P1CP e P1NP).

- Bone reabsorption markers

  deoxypyridinoline, collagen I C- e N-terminal telopeptides (CTX e NTX) , e tartrate resistent acid phosphatase (TRACP) isoforma 5b.

FIG. 1. A, Backtransformed reference curves for bone markers in boys (filled circles) and girls (open circles)

Rauchenzauner, M. et al.
J Clin Endocrinol Metab 2007;92:443-449

The Journal of Clinical Endocrinology & Metabolism

Bisphosponates

- bisphosphonates are the only drugs for which a substantial amount of experience is available in children, although even these drugs are not officially approved for paediatric use.
- treatment of children with moderate-to-severe osteogenesis imperfecta, and its beneficial effects on BMD have been reported in several observational studies ome studies also report a decreased fracture incidence
- less is known about the effectiveness and safety of bisphosphonates in children with secondary osteoporosis

- I bisfosfonati contenenti un gruppo aminico sono i più utilizzati in pediatria.

- In particolare, il neridronato è l'unico bisfosfonato somministrabile per via infusiva commercializzato in Italia con indicazione per osteogenesi imperfetta.

Protocollo terapeutico

- Terapia con 2 mg/kg per 4 anni ogni 3 mesi
- In seguito terapia con 1 mg/kg ogni 3 mesi

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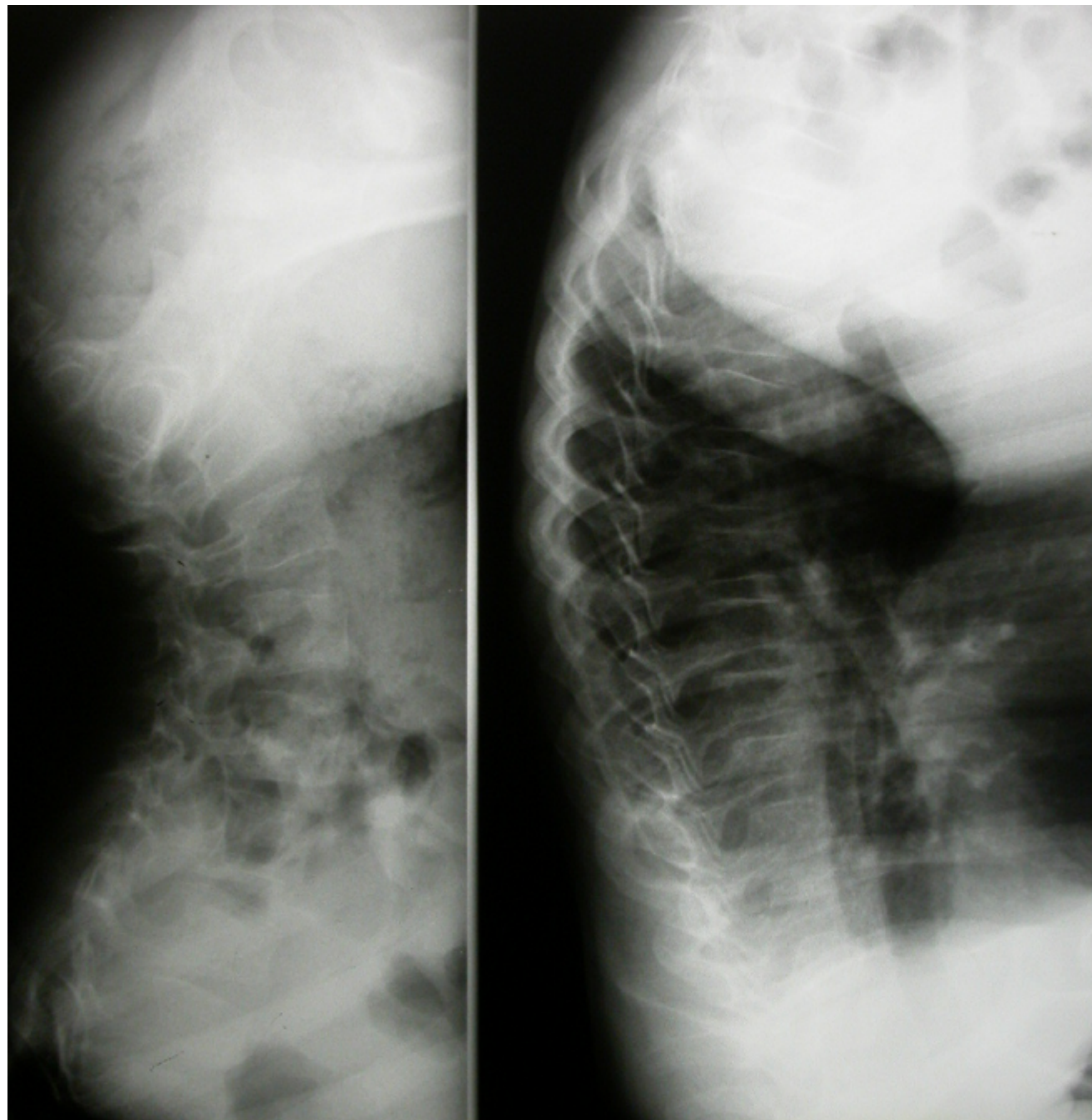
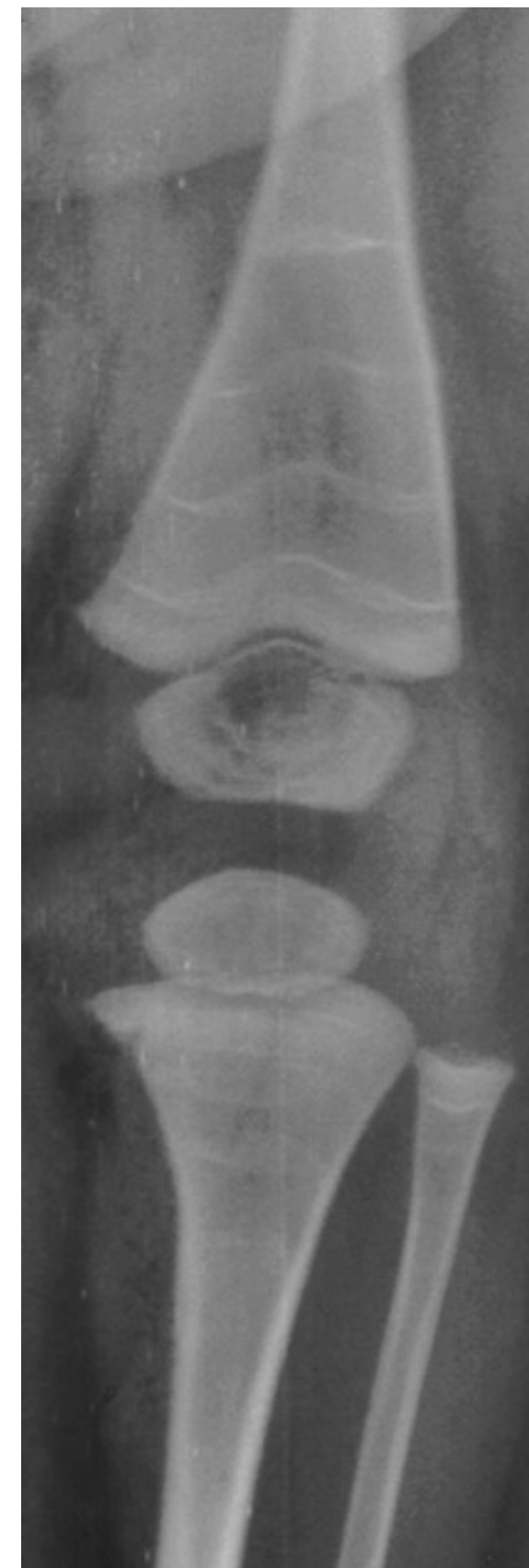
OI tipo III

ASSOCIAZIONE ITALIANA OSTEOGENESIS IMPERFECTA 1984 AS.IT.O.I

OI tipo I lieve

Before (1 m)

MC

6 m Rx (7 m)

Antoniazzi F et al. J Pediatr 2006

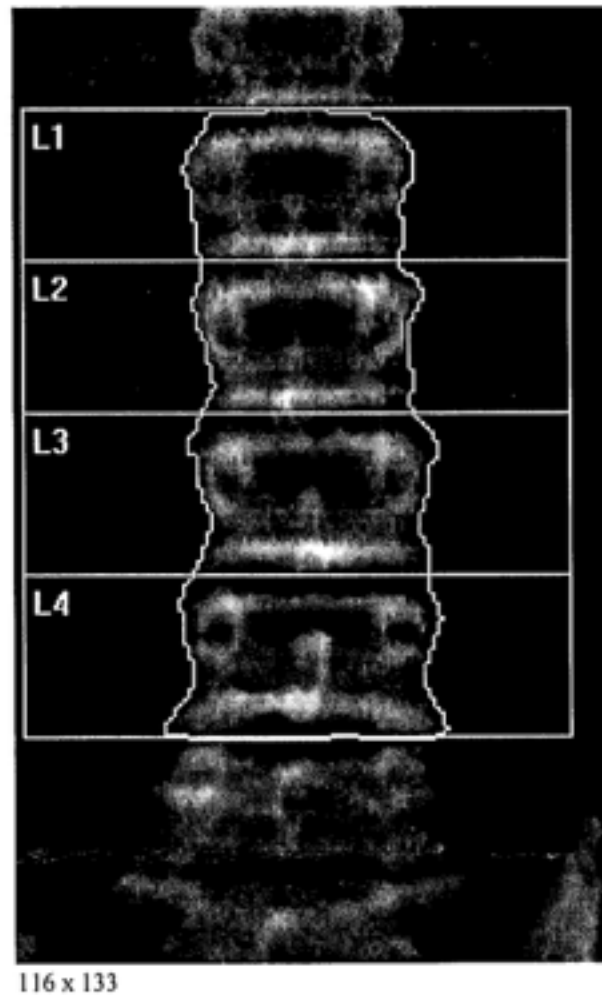
12 m Rx (13 m)

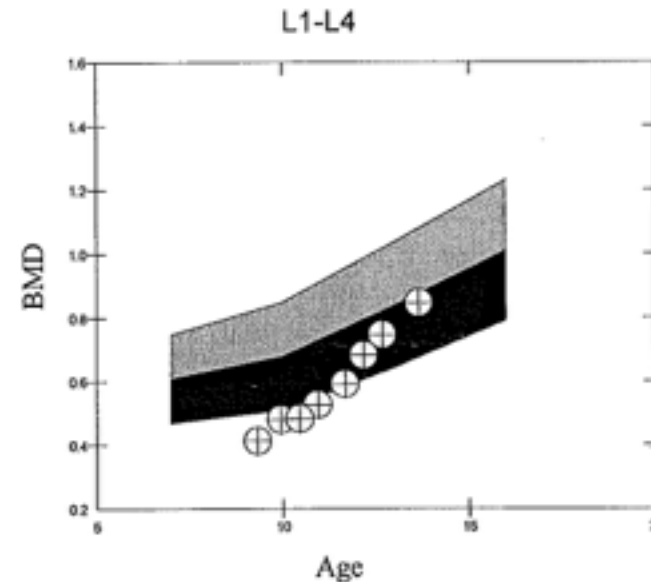
Antoniazzi F et al. J Pediatr 2006

MC

Name:	Sex: Male	Height: 168.0 cm
Patient ID:	Ethnicity: White	Weight: 59.0 kg
DOB:		Age: 13

Referring Physician:

116 x 133

Scan Information:

Scan Date: 10 October 2012 ID: A10101213
Scan Type: x Lumbar Spine
Analysis: 10 October 2012 12:58 Version 12.4
Lumbar Spine
Operator:
Model: Discovery A (S/N 81587)
Comment:

Reference curve and scores matched to White Male

Source: Hologic

DXA Results Summary: L1-L4

Scan Date	Age	BMD (g/cm²)	T - Score	BMD Change vs Baseline	BMD Change vs Previous
10.10.2012	13	0.846		105.3%#	13.4%*
19.10.2011	12	0.746		81.1%#	9.5%*
20.04.2011	12	0.681		65.4%#	15.3%*
20.10.2010	11	0.591		43.5%#	12.4%#
27.01.2010	10	0.526		27.6%*	9.2%*
29.07.2009	10	0.481		16.8%*	0.4%
28.01.2009	9	0.479		16.3%*	16.3%*
11.06.2008	9	0.412			

Total BMD CV 1.0%

J Bone Miner Metab (2012) 30:434–438
DOI 10.1007/s00774-011-0331-3

ORIGINAL ARTICLE

Children and adolescents treated with neridronate for osteogenesis imperfecta show no evidence of any osteonecrosis of the jaw

Evelina Maines · Elena Monti · Francesco Doro · Grazia Morandi · Paolo Cavarzere · Franco Antoniazzi

Table 1 Neridronate intravenous treatment in our patients

Type of OI	Patients (n)	Mean age at the start of treatment (years)	Mean length of treatment (years)
I	75	5.6 ± 3.6	6.7 ± 3.0
III	20	4.3 ± 4.3	6.9 ± 2.7
IV	4	9.6 ± 3.8	6.6 ± 5.5
Other types	3	2.0 ± 1.1	7.7 ± 2.7

Childs Nerv Syst (2012) 28:283–286
DOI 10.1007/s00381-011-1576-9

ORIGINAL PAPER

Osteopenia in children with cerebral palsy can be treated with oral alendronate

Muhammet Sukru Paksu · Sebahattin Vurucu · Abdulbaki Karaoglu · Alper Ozgur Karacalioglu · Ahmet Polat · Ozgur Yesilyurt · Bulent Unay · Ridvan Akin

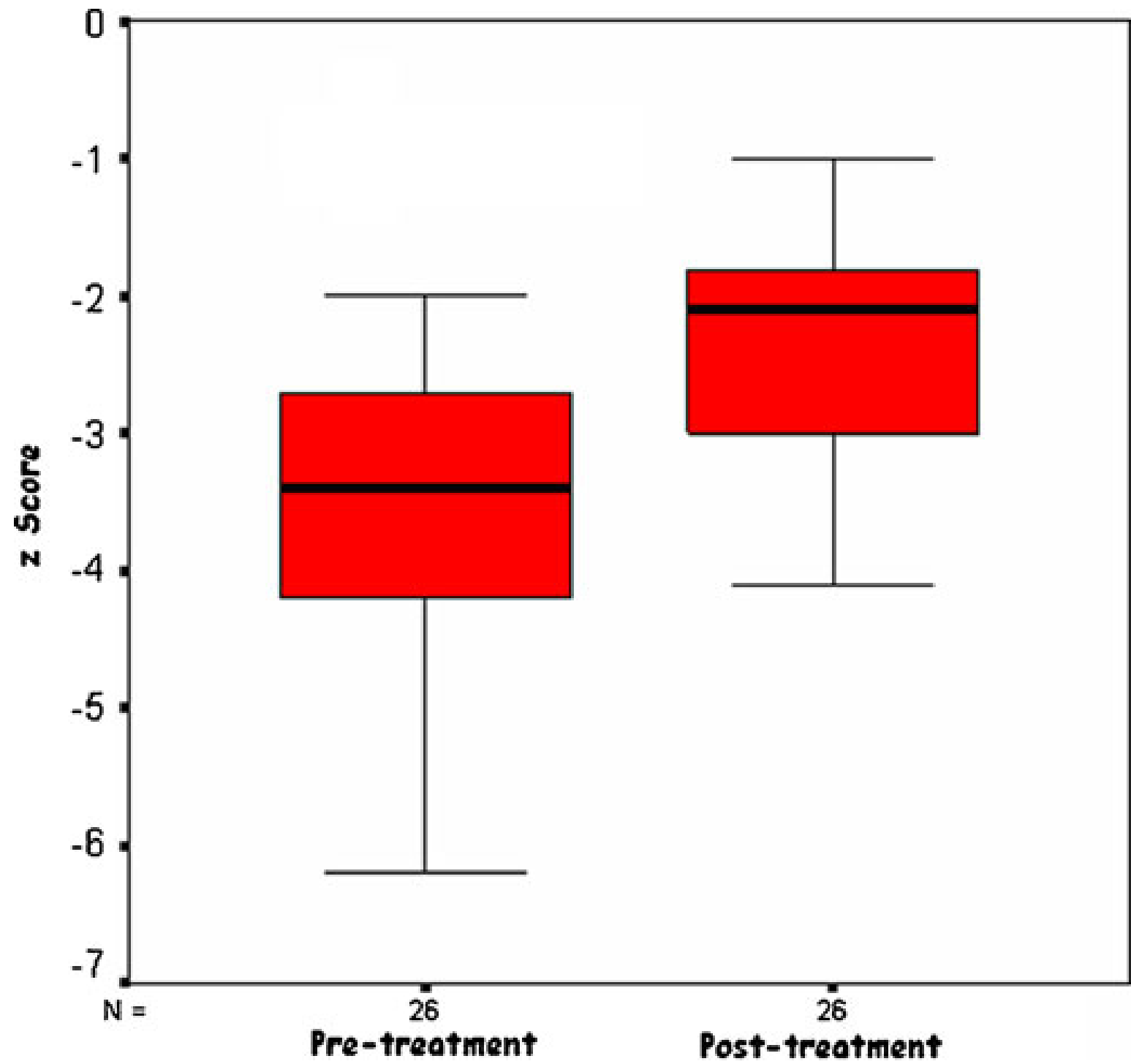



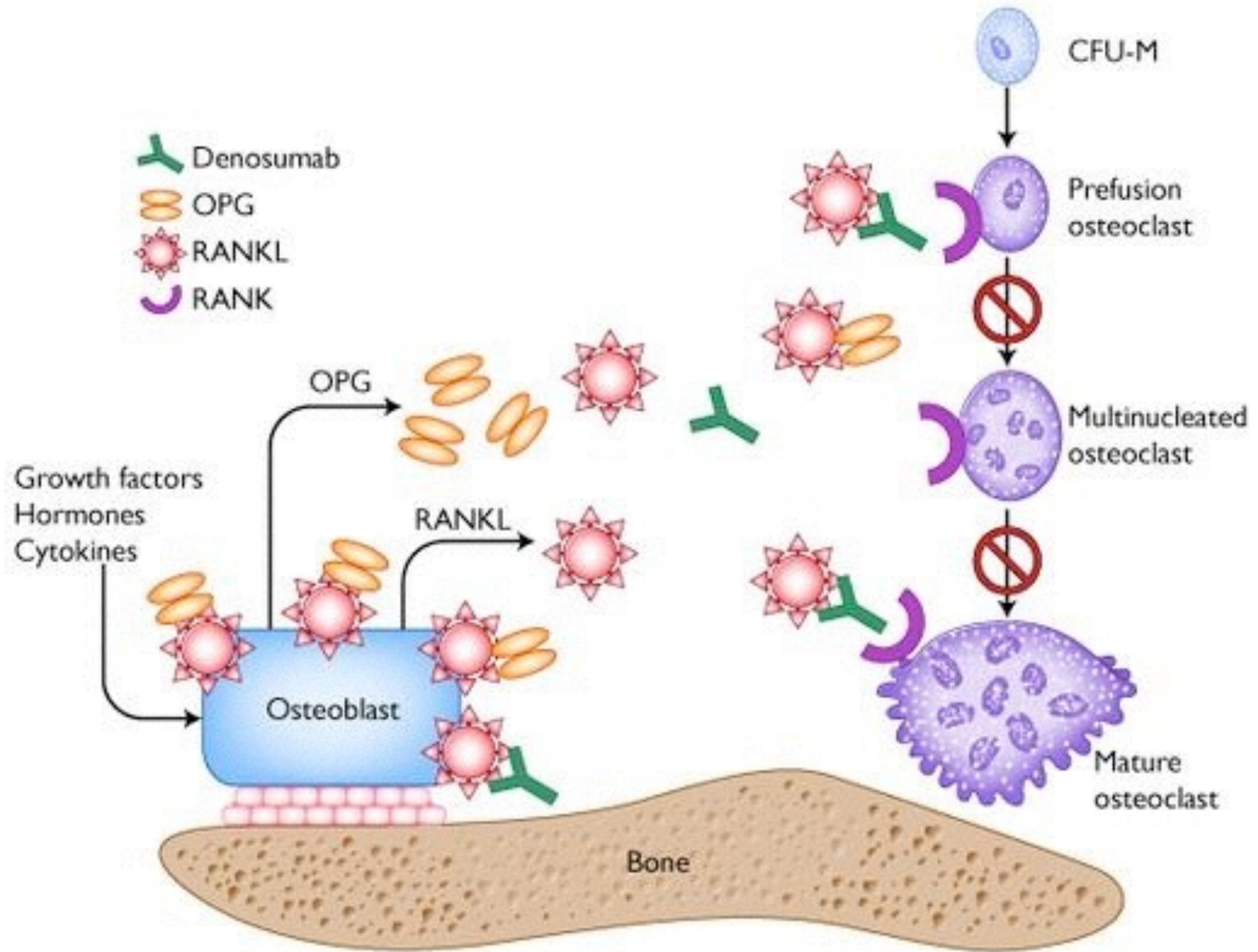
Fig. 2 Pre- and posttreatment *Z*-score

2012 Paksu Cerebral Palsy Osteoporosis

RANK-L inhibition (Denosumab)

Denosumab
OPG
RANKL
RANK
CFU-M
Prefusion osteoclast
Multinucleated osteoclast
Mature osteoclast
OPG
RANKL
Growth factors
Hormones
Cytokines
Osteoblast
Bone
© Current Medicine Group

J Musculoskelet Neuronal Interact 2012; 12(3):183-188

Original Article

First use of the RANKL antibody denosumab in Osteogenesis Imperfecta Type VI

O. Semler[1*], C. Netzer[2*], H. Hoyer-Kuhn[1], J. Becker[2], P. Eysel[3], E. Schoenau[1]

[1]Children's Hospital, University of Cologne, 50931 Cologne, Germany; [2]Institute of Human Genetics, University of Cologne, 50931 Cologne, Germany; [3]Department of Orthopaedic and Trauma surgery, University of Cologne, Cologne, Germany.
*These authors contributed equally

- This was the first use of denosumab in children with OI-VI.

  Denosumab was well tolerated, and laboratory parameters provided evidence that the treatment reversibly reduced bone resorption.

  Therefore, denosumab may be a new therapeutic option for patients with OI-VI.

EFFECT OF DENOSUMAB ON THE GROWING SKELETON IN OSTEOGENESIS IMPERFECTA

Heike Hoyer-Kuhn[1],M.D, Oliver Semler[1,2],M.D, Eckhard Schoenau[1,2],M.D

1 Children´s Hospital, University of Cologne, 50931 Cologne, Germany; 2 Cologne Center of Musculoskeletal Biomechanics, 50931 Cologne Germany

Images in Endocrinology Commentary

EFFECT OF DENOSUMAB ON THE GROWING SKELETON IN OSTEOGENESIS IMPERFECTA

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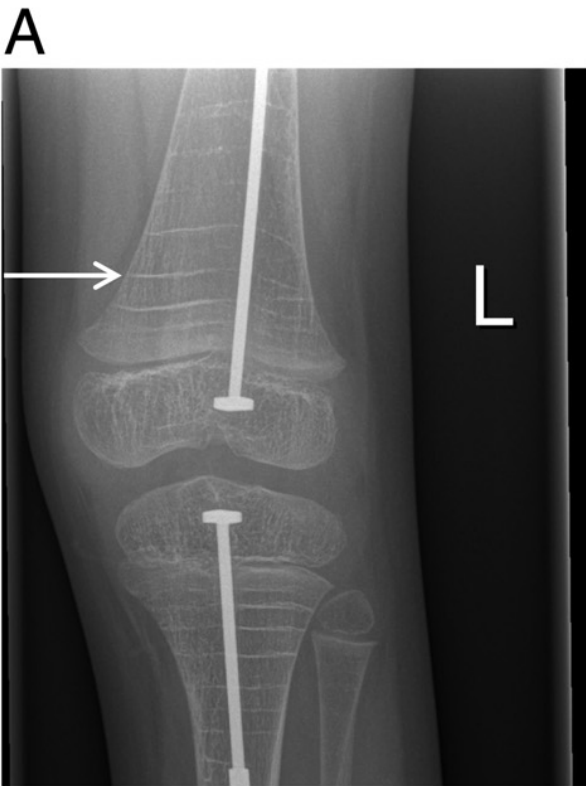
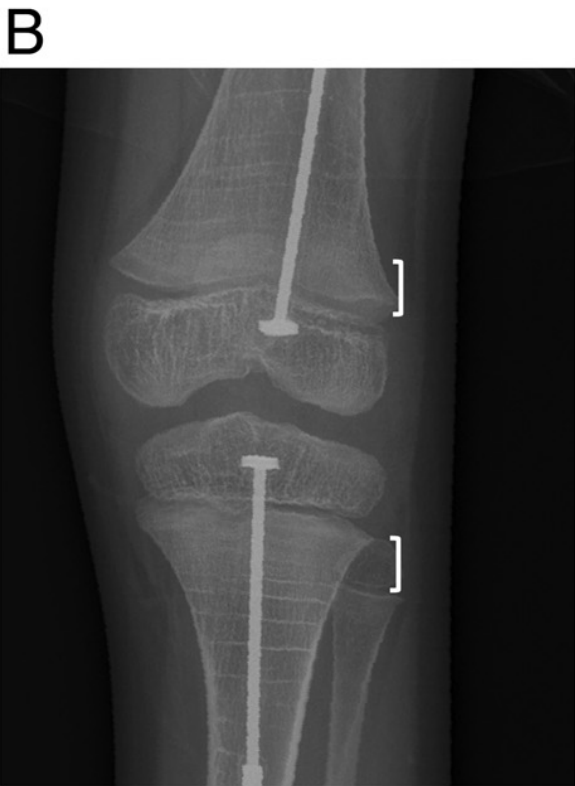
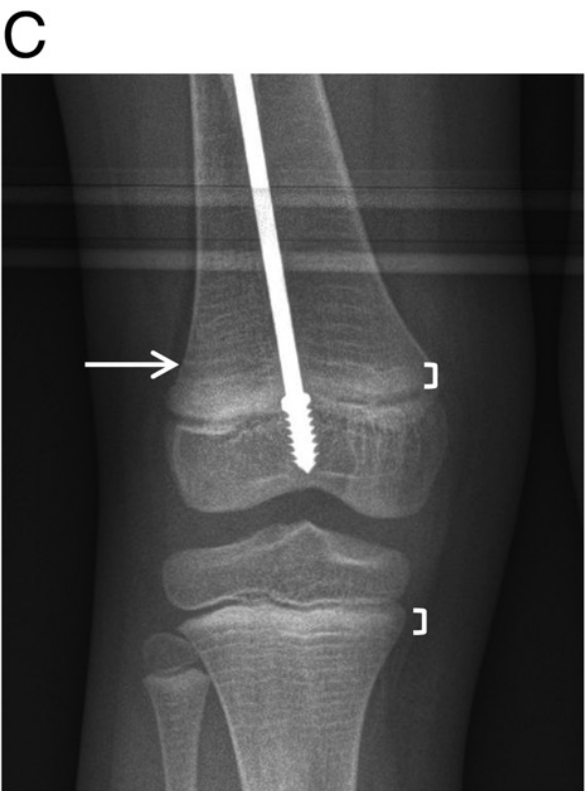
1 Children´s Hospital, University of Cologne, 50931 Cologne, Germany; 2 Cologne Center of Musculoskeletal Biomechanics, 50931 Cologne Germany

Images in Endocrinology Commentary

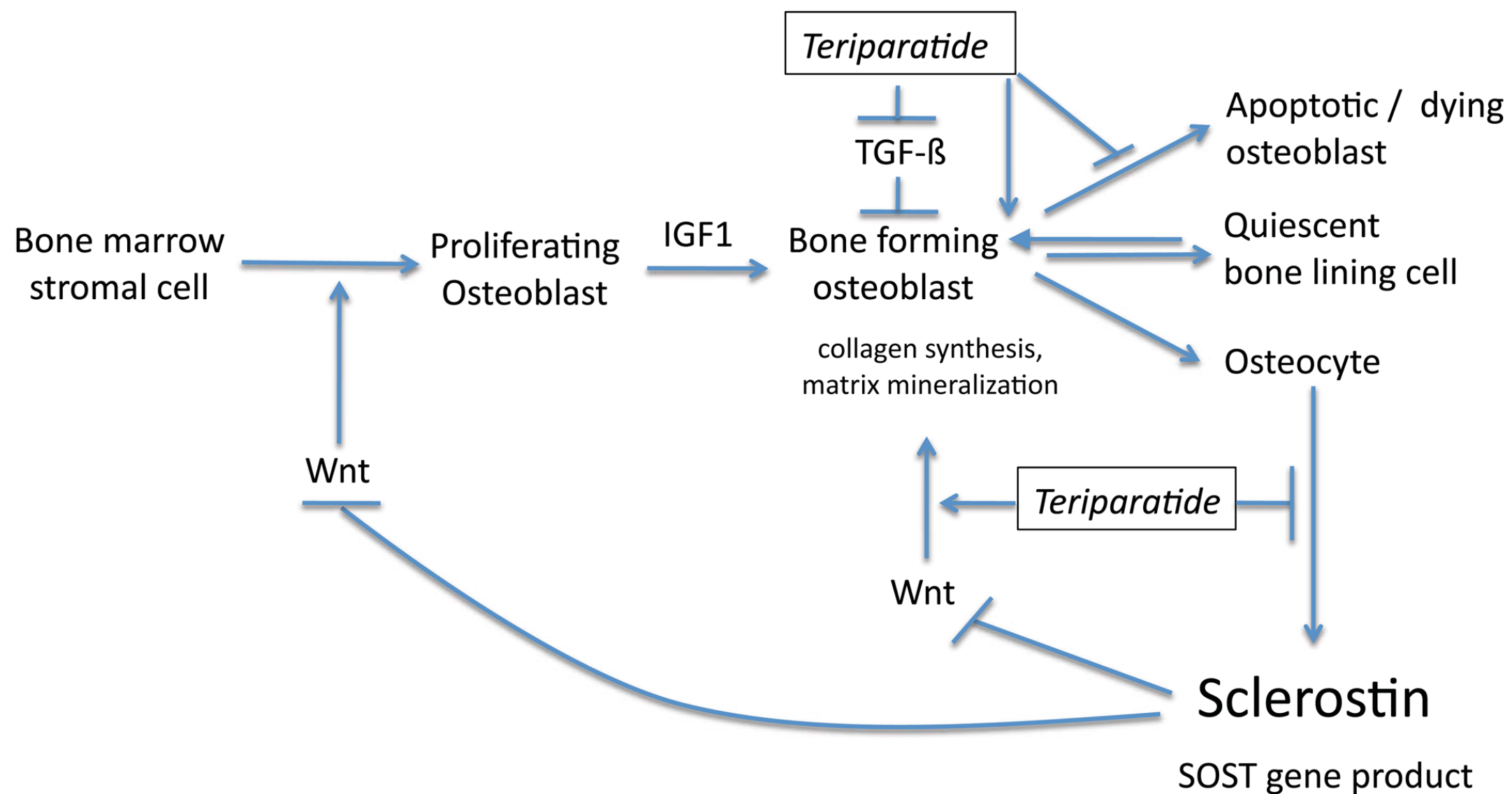
Pat 1:
Before treatment

A

Pat 1: After 8 months
denosumab

B

Pat 2: After 3
weeks denosumab

C

Pat 2: After 9
weeks denosumab

D

Figure 1. Radiographs of two children with classic Osteogenesis imperfecta treated with denosumab showing an increased metaphyseal density in the formed bone (square brackets) compared to the bisphosphonate induced "zebra lines" (arrows). patient 1 received 3 injections between radiographs 1A/1B, patient 2 received one dose before the radiographs 1C/1D.

2014 Hoyer-Kuhn OI denosumab

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Amy E. Riek: ariek@dom.wustl.edu; Dwight A. Towler: dtowler@dom.wustl.edu

Targeting The Osteoblast in Osteoporosis

2011 Riek Osteoporosis Treatment

Paratormone (PTH)

Parathyroid hormone (PTH)

- Parathyroid hormone (PTH) has two opposing effects on bone, depending on whether PTH is continuous or pulsed.
- Chronic administration or increased secretion of PTH in primary hyperparathyroidism stimulates bone resorption and leads to bone loss.
- Paradoxically, when PTH is administered intermittently it increases trabecular bone volume. Subcutaneously administered recombinant human PTH is currently used to treat adult osteoporosis. It cannot be used in children

Related Attending physician, page 476 Clinical medicine

Evaluation of teriparatide treatment in adults with osteogenesis imperfecta

Eric S. Orwoll,[1] Jay Shapiro,[2] Sandra Veith,[1] Ying Wang,[1] Jodi Lapidus,[1] Chaim Vanek,[1] Jan L. Reeder,[1] Tony M. Keaveny,[3,4] David C. Lee,[3] Mary A. Mullins,[5] Sandesh C.S. Nagamani,[5] and Brendan Lee[5,6]

[1]Oregon Health and Science University, Portland, Oregon, USA. [2]Kennedy Krieger Institute, Baltimore, Maryland, USA. [3]ON Diagnostics, Berkeley, California, USA. [4]Departments of Mechanical Engineering and Bioengineering, UC Berkeley, Berkeley, California, USA. [5]Baylor College of Medicine, Houston, Texas, USA. [6]Howard Hughes Medical Institute, Houston, Texas, USA.

2014 Orwoll OI PTH

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A Spine BMD (g/cm²)
Change from baseline (%)
6.1 (n = 29)*
4.7 (n = 30)*
2.8 (n = 27)*
2.2 (n = 32)
1.5 (n = 29)*
1.2 (n = 32)
Time on study (mo)
Treatment
Placebo

B Total hip BMD (g/cm²)
Change from baseline (%)
2.6 (n = 22)**
0.8 (n = 24)
0.5 (n = 29)
0.8 (n = 23)
–1.5 (n = 27)
–2.4 (n = 26)**
Time on study (mo)
Treatment
Placebo

C Femoral neck BMD (g/cm²)
Change from baseline (%)
1.2 (n = 23)
1.9 (n = 22)
0.4 (n = 29)
0.8 (n = 27)
0.2 (n = 24)
–1.8 (n = 25)
Time on study (mo)
Treatment
Placebo

D Forearm BMD (g/cm²)
Change from baseline (%)
0.9 (n = 21)*
0.5 (n = 22)
–0.3 (n = 25)
–0.7 (n = 20)
–0.7 (n = 24)
–1.3 (n = 25)*
Time on study (mo)
Treatment
Placebo

Figure 2
Bone density and vertebral strength. (**A**–**D**) Percent change from baseline in LS aBMD (g/cm²; **A**), TH aBMD (g/cm²; **B**), FN aBMD (g/cm²; **C**), and radial aBMD (g/cm²; **D**) in teriparatide- and placebo-treated patients (mITT population). Error bars denote SEM. Values shown are estimated least-squares mean of percent change. The number of patients with nonmissing percent change data at each time point is shown in parentheses. *$P < 0.05$, **$P < 0.001$ between treatment groups.

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Related Attending physician, page 476

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Figure 3

Spine QCT measures and FEA. Percent change from baseline in spinal trabecular vBMD (mg/cm^3), vertebral strength (N), and Φ (vertebral load/vertebral strength ratio) in teriparatide-and placebo-treated patients (mITT population) at 18 months. Error bars denote SEM. *$P < 0.05$ between treatment groups.

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Related Attending physician, page 476

Evaluation of teriparatide treatment in adults with osteogenesis imperfecta

Eric S. Orwoll,[1] Jay Shapiro,[2] Sandra Veith,[1] Ying Wang,[1] Jodi Lapidus,[1]
Chaim Vanek,[1] Jan L. Reeder,[1] Tony M. Keaveny,[3,4] David C. Lee,[3] Mary A. Mullins,[5]
Sandesh C.S. Nagamani,[5] and Brendan Lee[5,6]

[1]Oregon Health and Science University, Portland, Oregon, USA. [2]Kennedy Krieger Institute, Baltimore, Maryland, USA.
[3]ON Diagnostics, Berkeley, California, USA. [4]Departments of Mechanical Engineering and Bioengineering, UC Berkeley, Berkeley, California, USA.
[5]Baylor College of Medicine, Houston, Texas, USA. [6]Howard Hughes Medical Institute, Houston, Texas, USA.

A
P1NP (μg/l)
Change from baseline (%)
160
140
120
100
80
60
40
20
0
-20
-40
134.6 (n = 31)**
110.3 (n = 34)**
80.2 (n = 33)**
64.4 (n = 34)**
82.2 (n = 29)**
4.3 (n = 27)**
−1.5 (n = 36)**
−0.8 (n = 32)**
−4.0 (n = 35)**
−8.6 (n = 31)**
0 1 3 6 12 18
Time on study (mo)
Treatment
Placebo

B
Urine NTx (nM BCE/mM)
Change from baseline (%)
80
60
40
20
0
-20
63.6 (n = 34)**
57.1 (n = 30)**
49.6 (n = 29)*
34.1 (n = 32)*
18.3 (n = 33)
2.3 (n = 26)*
−1.3 (n = 35)
−3.5 (n = 32)*
1.9 (n = 34)**
1.9 (n = 31)**
0 1 3 6 12 18
Time on study (mo)
Treatment
Placebo

Figure 4
Bone remodeling markers. (**A** and **B**) Percent change from baseline in serum P1NP (μg/l; **A**) and urinary NTx (nM BCE/mM; **B**) in teriparatide and placebo-treated patients (mITT population) at baseline and at 6, 12, and 18 months. Error bars denote SEM. Values shown are estimated least-squares mean of percent change. The number of patients with nonmissing percent change data at each time point is shown in parentheses. *$P < 0.05$, **$P < 0.001$ between treatment groups.

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Adults with OI, particularly those with less severe disease (type I), displayed a teriparatide-induced anabolic response, as well as increased hip and spine aBMD, vertebral vBMD, and estimated vertebral strength.

Calcif Tissue Int
DOI 10.1007/s00223-013-9770-2

ORIGINAL RESEARCH

Teriparatide Treatment in Adult Patients with Osteogenesis Imperfecta Type I

Davide Gatti · Maurizio Rossini · Ombretta Viapiana · Maria Rosaria Povino · Saverio Liuzza · Elena Fracassi · Luca Idolazzi · Silvano Adami

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Table 2 Mean percent changes (±SD) versus baseline for BMD and bone markers after 6, 12, and 18 months of therapy

	n	6 months	12 months	18 months
Spine BMD	13	+2.2 ± 2.5*	+1.9 ± 2.4*	+3.5 ± 2.8**
Femoral neck BMD	10	−1.6 ± 2.7	−0.3 ± 3.4	−0.5 ± 5.6
P1NP	13	+295.6 ± 151.2**	+452.5 ± 315.4**	+359.5 ± 245.2**
bAP	13	+155.9 ± 106.6**	+248.0 ± 170.4**	+284.6 ± 164.1**
CTX	13	+214.5 ± 301.8**	+247.7 ± 146.6**	+184.9 ± 116.9**
DKK1	13	+21.3 ± 31.7*	+31.5 ± 40.5*	+51.6 ± 46.7**
Sclerostin	13	+1.8 ± 21.8	+8.9 ± 47.2	+18.1 ± 33.5

* $p < 0.05$, ** $p < 0.005$ versus baseline

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Paratormone (PTH)

Il PTH non può essere somministrato in

età pediatrica

WNT System

J Bone Miner Res. 2013 Jan;28(1):73-80. doi: 10.1002/jbmr.1717.

Sclerostin antibody improves skeletal parameters in a Brtl/+ mouse model of osteogenesis imperfecta.

Sinder BP, Eddy MM, Ominsky MS, Caird MS, Marini JC, Kozloff KM.

Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, University of Michigan Ann Arbor, MI, USA.

J Bone Miner Res. 2013 Jan;28(1):73-80. doi: 10.1002/jbmr.1717.

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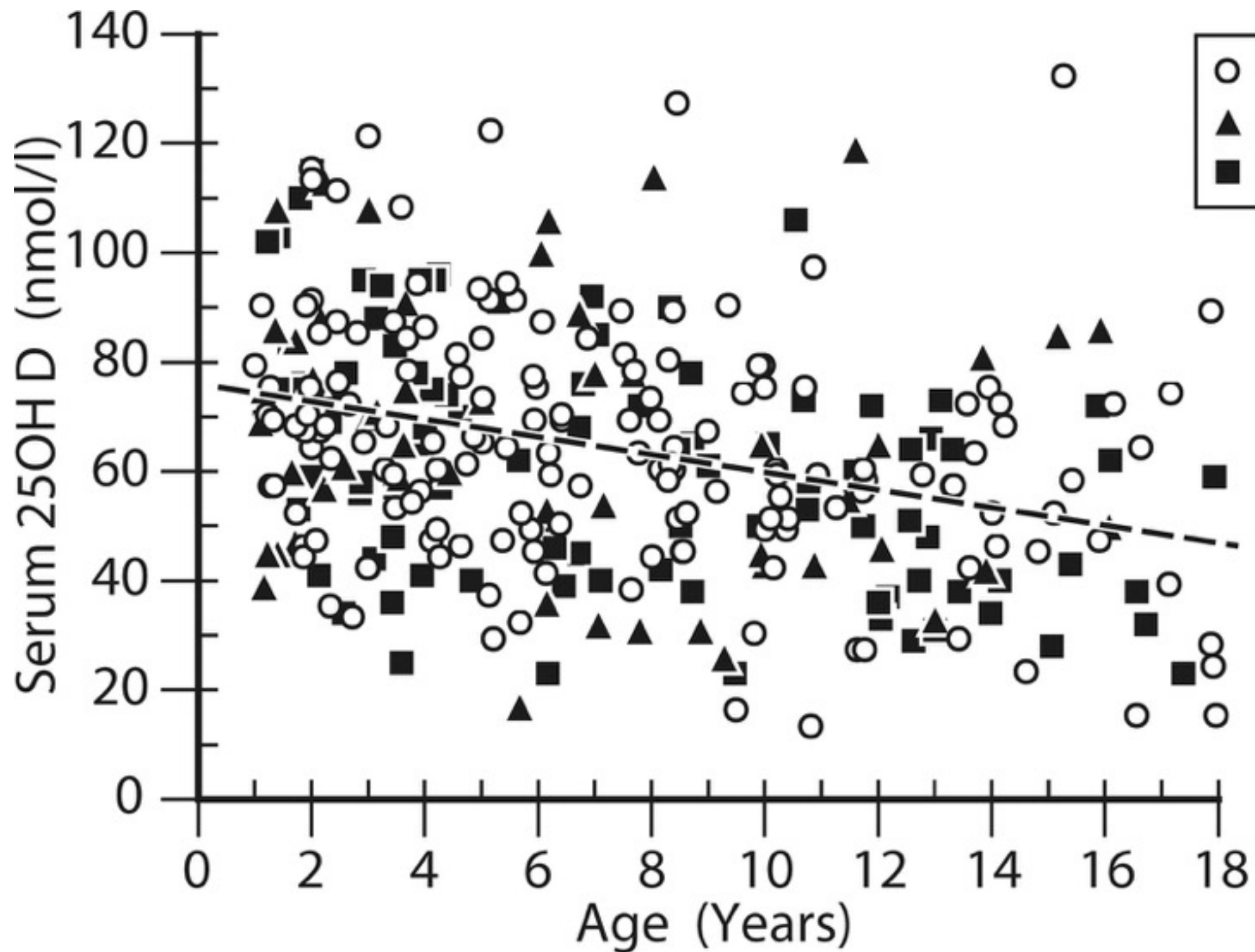
- In conclusion, short-term Scl-Ab was successfully anabolic in osteoblasts harboring a typical OI-causing collagen mutation and represents a potential new therapy to improve bone mass and reduce fractures in pediatric OI

Relationship between serum levels of 25OH D and age in the whole study group ($r = -0.33$; $P < 0.001$).

Edouard T et al. JCEM 2011;96:3193-3198

The Journal of Clinical Endocrinology & Metabolism

ORIGINAL ARTICLE

Endocrine Research

Predictors and Correlates of Vitamin D Status in Children and Adolescents with Osteogenesis Imperfecta

Thomas Edouard, Francis H. Glorieux, and Frank Rauch

Shriners Hospital for Children and McGill University (T.E., F.H.G., F.R.), Montréal, Québec, Canada H3G 1A6; and Endocrinology Service (T.E.), Ste-Justine Hospital and Université de Montréal, Montreal, Québec, Canada H3T 1C5

(*J Clin Endocrinol Metab* 96: 3193–3198, 2011)

Conclusion

This cross-sectional study provides some evidence that serum 25OH D levels are associated with LS-aBMD z-score in children and adolescents with OI types I, III, and IV. Randomized controlled trials are warranted to assess whether LS-aBMD z-scores can be increased by higher vitamin D intake.

Lethal

Normal

Type II

Type IV

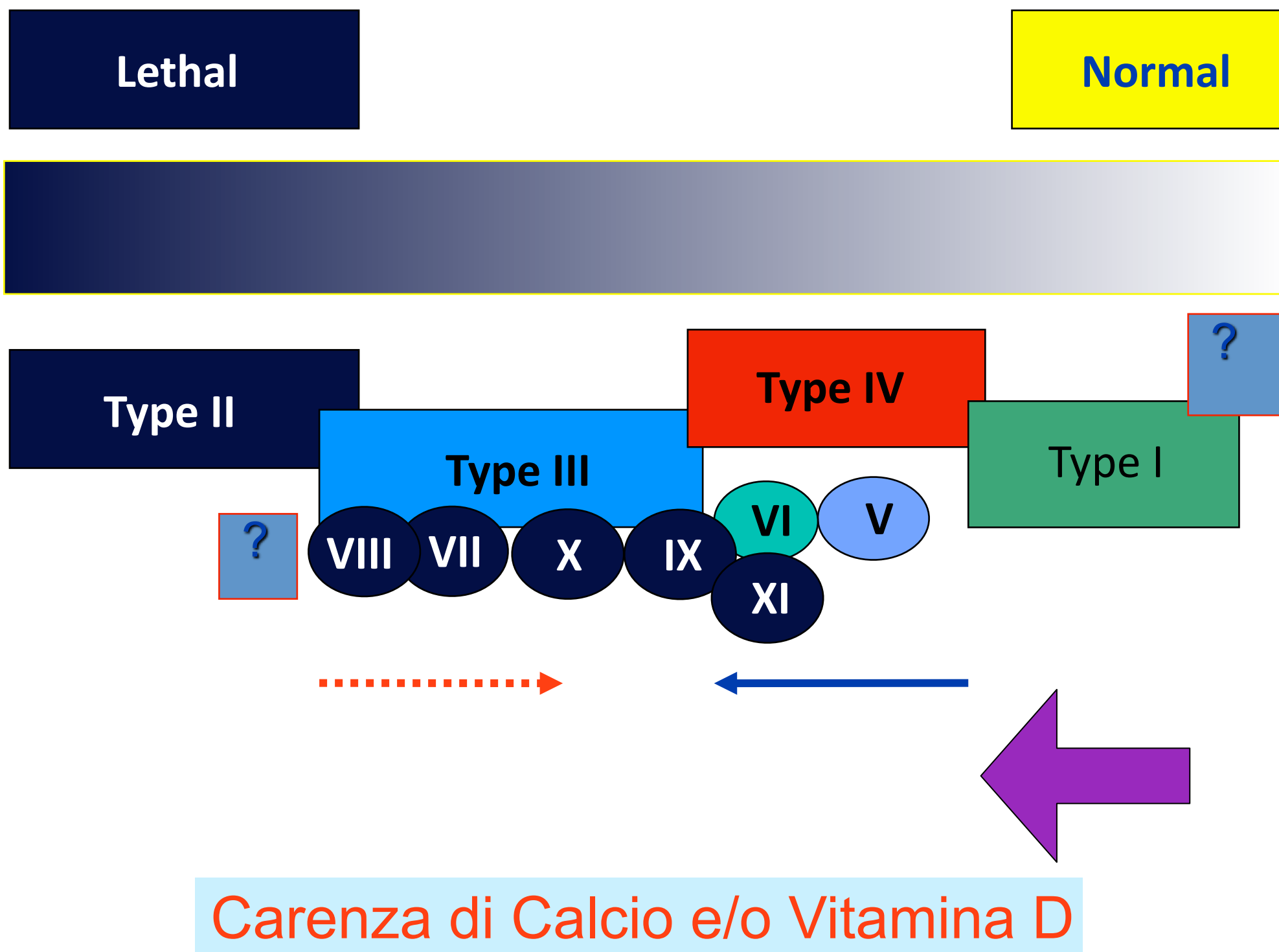
?

Type III

Type I

?

VIII VII X IX VI V XI

Carenza di Calcio e/o Vitamina D

Supplementazione con Vitamina D (e Calcio)

standard:

- Vitamina D 25000 UI al mese
- Calcio 500 mg al giorno

in caso di carenza accertata

- Vitamina D 50000-100000 UI al mese
- Calcio 1000 mg al giorno

Osteoporosis in Childhood conclusions

Osteoporosis has become an important paediatric illness and can affect patients in any paediatric subspecialty

Osteogenesis imperfecta is the most common form of primary osteoporosis in the paediatric age group and includes several forms with variable severity

Secondary osteoporosis is common in children with illnesses that involve chronic systemic inflammation, neuromuscular disabilities, or glucocorticoid treatment

Osteoporosis presents as low bone mineral density and an increased risk of fractures in the vertebrae and limb bones

Preventive measures include optimal control of the underlying illness, vitamin D supplementation and maintenance of weight-bearing activity

Bisphosphonates are increasingly being used in children, but data on their efficacy and safety in paediatric patients are inadequate, especially with regard to treatment of secondary osteoporosis